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Efficacy of Eravacycline in Obese Patients: Pooled Analysis of IGNITE1 and IGNITE4

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Abstract

Introduction: Risk factors for treatment failure (antibiotic failure or death) increase in certain groups of patients with complicated intra-abdominal infections.[1] Eravacycline (ERV), 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. The results of these RCTs met the primary endpoints of non-inferiority for clinical response.[2,3]

Research Question or Hypothesis: We sought to explore clinical outcomes in obese patients treated with eravacycline and comparator therapy with cIAI.

Study design: IGNITE1 and IGNITE4 were randomized, double-blind, non-inferiority phase 3 trials in patients > 18 years of age diagnosed with 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 or meropenem, respectively. Clinical cure 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 6 categories based on body mass index (BMI) (Table 1).

Results: The micro-ITT population consisted of 846 patients who grew at least one pathogen consistent with cIAI from an intra-abdominal culture. 415 patients received eravacycline vs 431 received comparator therapy.

Table 1. Clinical Outcomes Analyzed by BMI Category in the micro-ITT Population at TOC

Group[4]	BMI (median [min, max])	ERV % Cure (n/N)	CT % Cure (n/N)	Difference	95% CI (LL, UL)
All subjects	26.9 [17.1, 73.6]	88.7 (368/415)	89.3 (385/431)	-0.7	(-4.9, 3.6)
Obese Class III [BMI ≥ 40 kg/m^2]	41.1 [40, 73.6]	85.7 (6/7)	100 (4/4)	-14.3	(-51.3, 40.8)
Obese Class II [BMI 35-39.9 kg/m^2]	37.2 [35.1, 39.8]	93.9 (31/33)	89.7 (26/29)	4.3	(-11.1, 21.4)
Obese Class I [BMI 30-34.9 kg/m^2]	31.9 [30, 34.9]	82.0 (73/89)	88.5 (85/96)	-6.5	(-17.2, 3.8)
Overweight [BMI 25-29.9 kg/m^2]	27.2 [25, 29.98]	87.0 (127/146)	89.0 (130/146)	-2.1	(-9.8, 5.6)
Healthy weight [BMI 18.5-24.9 kg/m^2]	23 [18.5, 24.98]	94.0 (126/134)	89.8 (132/147)	4.2	(-2.4, 11.0)
Underweight [BMI < 18.5 kg/m^2]	17.4 [17.1, 18.48]	83.3 (5/6)	88.9 (8/9)	-5.6	(-49.6, 33.1)

ERV=eravacycline; CT=comparator therapy; n=number of subjects with clinical cure; N=number of subjects within a specific category; LL=lower limit; UL=upper limit

Conclusion: Eravacycline was effective in treating patients with cIAI regardless of BMI when dosed 1 mg/kg IV every 12 hours, based on total body weight. Eravacycline is an effective, empiric treatment option for cIAI comparable to carbapenems.

Introduction

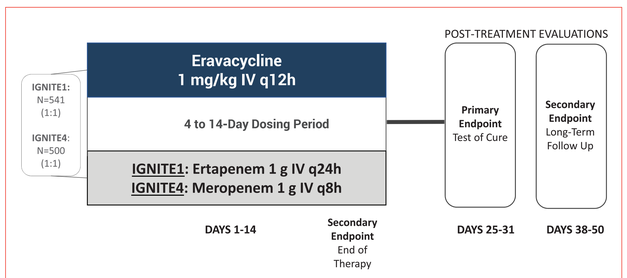
Eravacycline is a fully-synthetic fluorocycline antibacterial of the tetracycline class that has recently received the Food and Drug Administration's (FDA) approval for the treatment of complicated intra abdominal infections in patients ≥18 years of age.[5] It retains activity against the most common 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 obese patients (BMI > 30 kg/m^2) treated with eravacycline versus the comparator agents for cIAI.[4]

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 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

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 6 categories based on BMI (Obese, Class III, BMI > 40 kg/m^2; Obese, Class II, BMI 35-39.9 kg/m^2; Obese, Class I, BMI 30-34.9 kg/m^2; Overweight, BMI 25-29.9 kg/m^2; Healthy weight, BMI 18.5-24.9 kg/m^2; Underweight, BMI < 18.5 kg/m^2).[4] Clinical outcomes were analyzed by BMI in the micro-ITT population at TOC.

Results

Table 2. 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)
BMI, Median (Range), kg/mg^2	27.2 (17.2 - 73.6)	26.7 (17.1 - 46.4)
Weight, Median (Range), kg	80 (32 - 137)	80 (38 - 145)

Results (cont'd)

Figure 2. Distribution by Weight Category in the Eravacycline micro-ITT Population at Baseline (N=415)

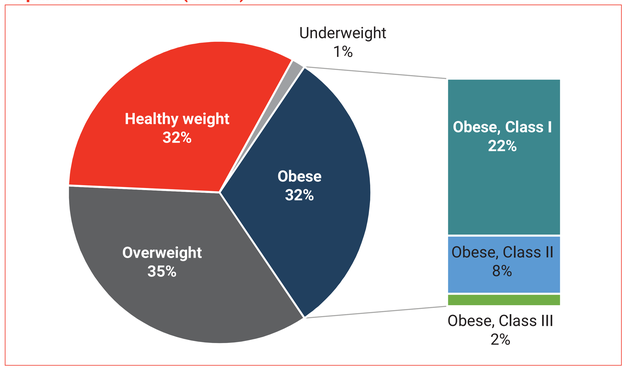
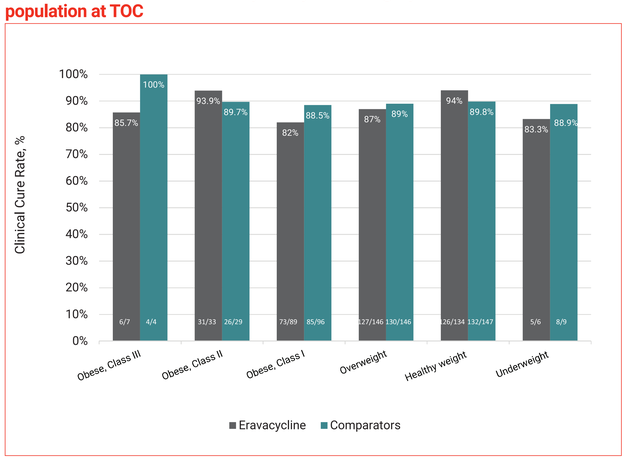


Figure 3. Clinical outcomes analyzed by BMI category in the micro-ITT population at TOC



Conclusions

Similar clinical cure rates were observed for eravacycline across all BMI categories, including the obese patient populations. Data demonstrate that eravacycline is an effective, empiric treatment option for cIAI, comparable to carbapenems when dosed 1 mg/kg total body weight.

References

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