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Pooled Analysis of Safety Data from Phase 2 and 3 Clinical Trials Evaluating Eravacycline in Complicated Intra-Abdominal Infections

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Abstract (revised)

Background: Eravacycline is a novel, fully-synthetic fluorocycline antibiotic that was evaluated in three comparator-controlled studies for the treatment of complicated intra-abdominal infections (cIAI). The objective of this analysis was to evaluate the safety profile of eravacycline 1 mg/kg IV q12h for the treatment of cIAI.

Methods: Pooled data from one phase 2 and two phase 3 (IGNITE1 and IGNITE4) clinical trials in cIAI were analyzed. Patients in the trials were randomized to receive eravacycline 1 mg/kg IV q12h, ertapenem 1 g IV q24h, or meropenem 1 g IV q8h for 4-14 days. Overall treatment-emergent adverse events (TEAEs), serious TEAEs, and laboratory assessments were evaluated.

Results: 576 patients were treated with eravacycline 1 mg/kg IV q12h and 547 patients with comparators (ertapenem and meropenem). Demographic and baseline characteristics were similar among the groups. Overall summary and common TEAEs are presented in Table 1. None of the serious TEAEs or those leading to death were related to the study drug. Clinically notable laboratory abnormalities were relatively uncommon and occurred at similar frequencies in eravacycline- and comparator-treated patients.

Table 1. Overall Summary of Treatment Emergent Adverse Events – Eravacycline Phase 2 and Phase 3 Clinical Studies

	Eravacycline 1 mg/kg IV q12h N=576 n (%)	Comparators* N=547 n (%)
Any TEAEs	217 (37.7)	152 (27.8)
Nausea	40 (6.9)	5 (0.9)
Infusion site reactions	39 (6.8)	10 (1.8)
Vomiting	20 (3.5)	13 (2.4)
Wound infection	15 (2.6)	6 (1.1)
Diarrhea	13 (2.3)	8 (1.5)
Anemia	11 (1.9)	16 (2.9)
Pyrexia	11 (1.9)	11 (2.0)
Hypertension	9 (1.6)	13 (2.4)
Treatment-related TEAEs	71 (12.3)	20 (3.7)
TEAEs Leading to Discontinuation from Study Drug	9 (1.6)	12 (2.2)
Serious TEAEs	33 (5.7)	33 (6.0)
TEAEs Leading to death	7 (1.2)	7 (1.3)

*Comparators include ertapenem 1 g IV q24h and meropenem 1 g IV q8h

Conclusion: This pooled analysis demonstrated that eravacycline 1 mg/kg IV q12h was generally well tolerated for the treatment of cIAI when compared to ertapenem and meropenem. Results of the analysis are consistent with those of individual clinical studies and no new safety signals were identified.

Introduction

Eravacycline is a fully-synthetic fluorocycline antibacterial of the tetracycline class that has recently received Food and Drug Administration (FDA) approval for the treatment of complicated intra abdominal infections[1]. It retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)[2,3]. Eravacycline has activity against a broad range of Gram-negative, Gram-positive and anaerobic strains.

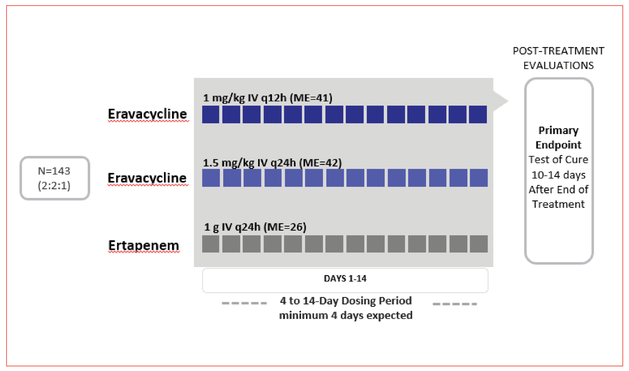
Efficacy of eravacycline for the treatment of complicated intra-abdominal infections (cIAI) was demonstrated in three controlled clinical trials: one Phase 2 and two Phase 3 clinical trials (IGNITE1 and IGNITE4)[4-6]. The objective of this analysis was to evaluate the safety profile of eravacycline 1 mg/kg IV q12h for the treatment of cIAI by pooling safety data from the three trials.

Methods

A phase 2, randomized, double-blind, active-control study was conducted to assess the efficacy and safety of two dose regimens of eravacycline (1 mg/kg IV q12h and 1.5 mg/kg IV q24h) vs. ertapenem (1 g IV q24h) in patients 18-75 years of age who had a confirmed diagnosis of cIAI that required urgent surgical or percutaneous intervention (Figure 1). Test-of-cure (TOC) evaluations occurred 10 to 14 days after the last dose of study drug. A follow-up visit occurred 28 to 42 days after the last dose of study drug.

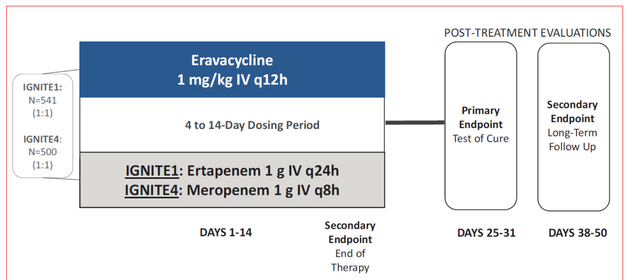
Methods (cont'd)

Figure 1. Eravacycline Phase 2 Clinical Trial in cIAI Study Design



IGNITE1 and IGNITE4 were 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 (Figure 2). The primary endpoint was clinical response in the microbiological intent-to-treat (micro-ITT) population at the TOC visit, 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 margins for IGNITE1 and IGNITE4 were 10% and 12.5%, respectively.

Figure 2. IGNITE1 and IGNITE4 Study Design



Key Inclusion Criteria

- Male or female subjects 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 (<30 mL/min for Phase 2)
- 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 ertapenem, 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 (IGNITE1 and IGNITE4)
- Known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs

Safety assessment included adverse events, laboratory tests, vital signs, electrocardiograms, and physical examinations. The safety population included all randomized patients who received any amount of study drug.

Results

- A total of 576 patients treated with eravacycline 1 mg/kg IV q12h and 547 patients treated with comparators were evaluated for adverse events (Table 1). The median age of patients treated with eravacycline was 54 years (range 18-93); 28.3% were ≥ 65 years of age.
- The eravacycline treated population included 28% obese patients (BMI ≥30 kg/m^2).
- The eravacycline treated population included 7.6% with baseline moderate to severe renal impairment.

Table 2. Demographics and Baseline Characteristics – Phase 2, IGNITE1 and IGNITE4 Clinical Trials

	Eravacycline[a] N = 576 n (%)	Comparators[b] N = 547 n (%)
Age (years)		
< 65	413 (71.7)	392 (71.7)
≥ 65	163 (28.3)	155 (28.3)
≥ 75	59 (10.2)	69 (12.6)
Gender, Male	337 (58.5)	313 (57.2)
Race, Caucasian	548 (95.1)	528 (96.5)
APACHE II Score		
< 10	466 (80.9)	432 (79)
≥ 10	108 (18.8)	112 (20.5)
Renal Impairment - CrCL (mL/min)		
Moderate to Severe (15 - < 60)	44 (7.6)	35 (6.4)
Normal to Mild (≥ 60)	521 (90.5)	498 (91)
Augmented (≥ 130)	199 (34.5)	183 (33.5)
Hepatic Impairment		
Child-Pugh Class A	418 (72.6)	382 (69.8)
Child-Pugh Class B	77 (13.4)	84 (15.4)
Child-Pugh Class C	--	--

[a]Eravacycline 1 mg/kg IV q12h dose
[b]Comparators: Ertapenem 1 g q24h IV and Meropenem 1 g q8h IV

Results (cont'd)

- A summary of treatment-emergent adverse events (TEAEs) among cIAI patients treated with eravacycline and comparators is presented in Table 2. The most common TEAEs in the eravacycline group were gastrointestinal disorders.
- None of the serious TEAEs or deaths in either the eravacycline or comparator group were reported as related to study drug.

Table 3. Overall Summary of TEAEs in cIAI – Phase 2, IGNITE1, IGNITE4 Clinical Trials

TEAE Category	Eravacycline[a] N = 576 n (%)	Comparators[b] N = 547 n (%)
TEAE	217 (37.7)	152 (27.8)
Severe TEAE	28 (4.9)	31 (5.7)
Treatment-related TEAE	71 (12.3)	20 (3.7)
TEAE Leading to Discontinuation from Study Drug	9 (1.6)	12 (2.2)
Serious TEAE	33 (5.7)	33 (6)
Serious TEAE Related to Study Drug	--	--
TEAE Leading to Death	7 (1.2)	7 (1.3)

[a]Eravacycline 1 mg/kg IV q12h dose
[b]Comparators: Ertapenem 1.0 g q24h IV and Meropenem 1.0 g q8h IV

Table 4. TEAEs Occurring in ≥ 2% of Subjects in Either Treatment Group in Controlled Clinical Trials for cIAI

TEAEs	Eravacycline[a] N = 576 n (%)	Comparators[b] N = 547 n (%)
Nausea	40 (6.9)	5 (0.9)
Infusion site reactions[c]	39 (6.8)	10 (1.8)
Vomiting	20 (3.5)	13 (2.4)
Wound infection	15 (2.6)	6 (1.1)
Diarrhea	13 (2.3)	8 (1.5)
Anemia[d]	11 (1.9)	16 (2.9)
Pyrexia	11 (1.9)	11 (2.0)
Hypertension[e]	9 (1.6)	13 (2.4)

[a]Eravacycline 1 mg/kg IV q12h dose
[b]Comparators: Ertapenem 1 g q24h IV and Meropenem 1 g q8h IV
[c]infusions site reactions include: catheter/vessel puncture site pain, infusion site extravasation, infusion/injection site phlebitis, infusion site thrombosis, injection site erythema, phlebitis, phlebitis superficial, and thrombophlebitis.
[d]Anemia includes: anemia, anemia postoperative, and normochromic normocytic anemia.
[e]Hypertension includes: blood pressure increased, essential hypertension, hypertension, and systolic hypertension.

- Clinically notable laboratory abnormalities, including liver function test and pancreatic elevations, were relatively uncommon and occurred at similar frequencies in eravacycline- and comparator-treated patients. Infusion site reactions never led to study drug discontinuation and were managed by increased infusion duration as well as decreasing concentration of study drug.
- Comparisons with the 1.5 mg/kg q24h group were limited by the small number of subjects in this group. However, the overall results in this group were generally similar.

Conclusions

This pooled analysis demonstrated that eravacycline 1 mg/kg IV q12h was generally well tolerated for the treatment of cIAI when compared to ertapenem and meropenem. No new safety signals were identified in this analysis, which demonstrates the consistent safety profile of eravacycline.

References

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2. Xiao X, et al. *J Med Chem* 2012;55:597-605.
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4. Solomkin JS, Ramesh MK, Cesnauskas G, et al. Phase 2, randomized, double-blind study of the efficacy and safety of two dose regimens of eravacycline versus ertapenem for adult community-acquired complicated intra-abdominal infections. *Antimicrob Agents Chemother.* 2014;58(4):1847-1854.
5. Solomkin J, Evans D, Slepavicius A, et al. Assessing the Efficacy and Safety of Eravacycline vs Ertapenem in Complicated Intra-abdominal Infections in the Investigating Gram-Negative Infections Treated with Eravacycline (IGNITE 1) Trial: A Randomized Clinical Trial. *JAMA Surg.* November 2016.
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