Results of IGNITE4: A Phase 3 Study to Evaluate the Efficacy and Safety of Eravacycline versus Meropenem in Complicated Intra-abdominal Infections

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Abstract

Background: IGNITE4 is a global, multicenter, double-blind, non-inferiority phase 3 trial conducted to evaluate eravacycline for the treatment of complicated intra-abdominal infections (cIAI).

Materials/methods: Patients were randomized (1:1) to receive eravacycline (1 mg/kg IV q12h) or meropenem (1g IV q8h) for up to 14 days. Clinical outcome at the test of cure visit (TOC, 25-31days after randomization) was the primary efficacy endpoint.

Results: 500 patients were randomized [199 (39.8%) complicated appendicitis, 301 (60.2%) other diagnoses including complicated cholecystitis (24%) intestinal perforation (7%), stomach/duodenal perforation (11%)]. Treatment arms were well matched. Baseline isolates were cultured from 400 patients, including *Escherichia coli* (260), *Klebsiella spp.* (62), *Acinetobacter spp* (12) *Pseudomonas aeruginosa* (39), *enterococci* (146), *streptococci* (152), *Staphylococcus aureus* (110) and *Bacteroides spp* (182).

Clinical Outcomes at TOC:

Population (N)	Eravacycline % Cure (n)	Meropenem % Cure (n)	Difference	95% CI
Micro-ITT[1] (400)	90.8 (177)	91.2 (187)	-0.5	(-6.3, 5.3)
MITT[2] (499)	92.4 (231)	91.6 (228)	0.8	(-4.1, 5.8)
CE[3] (456)	96.9 (218)	96.1 (222)	0.8	(-2.9, 4.5)

[1]Micro-ITT: at least one baseline pathogen, [2]MITT: received study drug, [3]CE: followed key trial components

For the micro-ITT population, 7 subjects in each arm were clinical failures at TOC manifested as: persistence of clinical symptoms (Eravacycline=1, Meropenem=3), unplanned surgical procedure (5 each), wound infection (Eravacycline=2, Meropenem=0), and rescue antibiotics (6 each).

There were no study-drug related SAEs. Overall 37.2% and 30.9% of patients in the eravacycline and meropenem arms, respectively reported at least 1 TEAE. The most common AEs in both groups were infusion site reactions and gastro-intestinal, occurring in less than 5% of patients.

Conclusions: This study met its primary efficacy endpoint, demonstrating non-inferiority of eravacycline to meropenem in the treatment of cIAI. Treatment with eravacycline was well-tolerated. These data support the use of eravacycline for the treatment of cIAI, including infections caused by pathogens resistant to other antibiotics.

This study was registered with both ClinicalTrials.gov (NCT02784704) and EudraCT (2016-002208-21) and was funded by Tetraphase Pharmaceuticals.

Background

Eravacycline is a novel, fully-synthetic fluorocycline antibiotic that has completed phase 3 clinical development for patients with complicated intra-abdominal infections (cIAI) and is under regulatory review by the Food and Drug Administration (FDA) and European Medicines Agency (EMA). Eravacycline has potent *in-vitro* activity against a broad range of susceptible and multidrug-resistant (MDR) Gram-positive and Gram-negative aerobic and anaerobic strains (including *Staphylococcus aureus, Enterococcus faecium, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii* and *Bacteroides spp.*). It retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)[1-4]. The objective of this study was to assess the efficacy and safety of eravacycline compared with meropenem in subjects hospitalized for cIAI requiring surgery.

Methods

IGNITE4 is a phase 3 randomized, double-blind, double-dummy, multicenter, prospective study designed to assess the efficacy and safety of twice-daily intravenous eravacycline (1 mg/kg every 12 hours) compared with meropenem (1g every 8 hours) 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 12.5% non-inferiority margin in the microbiological intent-to-treat (micro-ITT) population.

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

Figure 1. Study Design

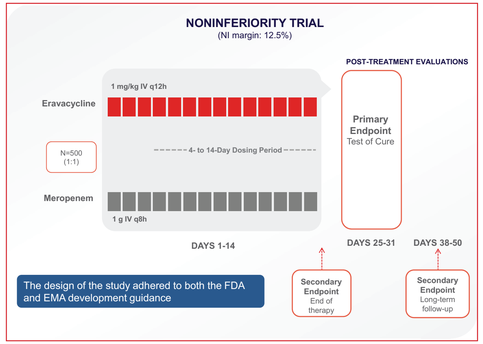


Table 1. Demographics and Baseline Characteristics MITT population

	Eravacycline (N=250)	Meropenem (N=249)
Gender, male, n (%)	139 (55.6)	129 (51.8)
Race, White, n (%)	249 (99.6)	249 (100)
Age, n (%)		
<65	180 (72)	174 (69.9)
≥65	70 (28)	75 (30.1)
APACHE II score, n (%)		
<10	202 (80.8)	200 (80.3)
≥10	48 (19.2)	49 (19.7)
≥15	7 (2.8)	11 (4.4)
Primary Disease Diagnosis, n (%)		
Complicated Appendicitis	99 (39.6)	99 (39.8)
Other cIAI	151 (60.4)	150 (60.2)

MITT = modified intent-to-treat

Figure 2. Baseline Pathogens Distribution

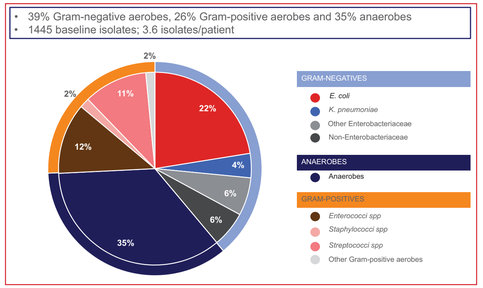


Figure 3. Efficacy Overview

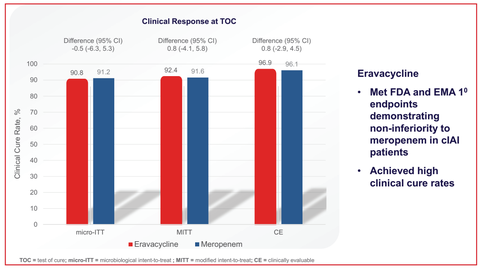
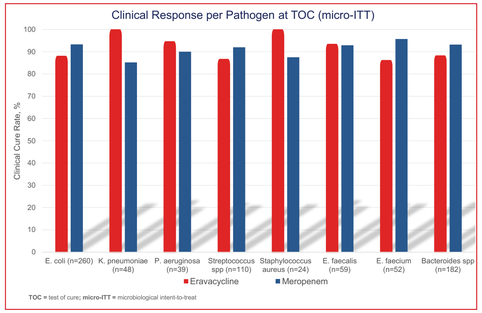


Table 2. Safety Overview

	Eravacycline (N=250)	Meropenem (N=249)
TEAEs Occurring in >2 % of Subjects, n (%)		
Nausea	12 (4.8)	2 (0.8)
Vomiting	9 (3.6)	5 (2)
Infusion site phlebitis	8 (3.2)	1 (0.4)
Diarrhea	6 (2.4)	3 (1.2)
Anemia	3 (1.2)	6 (2.4)

TEAE: Treatment Emergent Adverse Event

Figure 4. Secondary Efficacy Endpoint



Conclusions

The data from this trial demonstrated non-inferiority of eravacycline to meropenem in the treatment of complicated intra-abdominal infection. The results of this phase 3 study are consistent with the favorable efficacy, safety and tolerability previously observed in published studies comparing eravacycline to ertapenem in cIAI[5,6]. These data further suggest that, if approved, eravacycline may provide an additional monotherapy treatment option for patients with polymicrobial cIAI and may provide an alternative to carbapenems in cases where Gram-negative resistance is a concern.

References

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