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Results in Higher-Risk Subgroups from IGNITE1: A Phase 3 Study to Evaluate the Efficacy and Safety of Eravacycline versus Ertapenem in Complicated Intra-Abdominal Infections

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Abstract

Background: Eravacycline (ERV) is a novel fluorocycline that is highly active in vitro against multi drug-resistant bacterial pathogens encountered with increasing frequency in complicated intra-abdominal infections (cIAI). Overall results from IGNITE1, a study conducted to evaluate the efficacy and safety of ERV in the treatment of cIAI, have recently been reported. Here we report additional results in several subgroups that might be at higher risk of poor outcome.
Methods: In this randomized, double-blind, non-inferiority phase 3 trial, patients with documented cIAI were randomized (1:1) to either ERV (1.0 mg/kg IV q12h) or ertapenem (ETP, 1g IV daily). Treatment duration was up to 14 days. Clinical, microbiological, and safety outcomes were recorded. Clinical outcome at the test of cure (TOC) visit, approximately 28 days after randomization, was the primary efficacy endpoint in the microbiological-intent-to-treat (micro-ITT) population. For treatment failures, adequacy of source control was reviewed by an expert panel. The effects of age, APACHE II score, and intra-abdominal abscesses on clinical outcome were examined.
Results: 541 patients were randomized. Treatment arms were well matched. The micro-ITT population was comprised of 446 patients who grew at least one pathogen consistent with cIAI in baseline cultures.
Clinical outcomes by subgroup of interest in the micro-ITT population at TOC were:

Group (N)	ERV % Cure	ETP % Cure	Difference	95% "CI (LL, UL)
All (446)	86.8	87.6	-0.8	(-7.1, 5.5)
Age				
<65 (308)	88.6	89.3	-0.7	(-8.0, 6.4)
≥65 (138)	83.1	83.6	-0.5	(-13.0, 12.2)
≥75 (59)	92.9	90.3	2.5	(-14.2, 18.6)
APACHE II				
<10 (347)	86.7	89.1	-2.4	(-9.4, 4.6)
≥10 (99)	87.2	82.7	4.5	(-10.2, 18.7)
Abscess				
None (183)	86.6	89.1	-2.5	(-12.7, 7.0)
≥1 (263)	87.0	86.4	0.6	(-7.7, 9.0)

Conclusions: This study met its primary efficacy endpoint, demonstrating non-inferiority of ERV to ETP in the treatment of cIAI. ERV was also effective in treating subgroups of patients who might be at higher risk of poor outcome from cIAI, including the elderly, those with higher acuity illness, and those with abscesses

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Introduction

Complicated intra-abdominal infections (cIAI) infections are a frequent problem in clinical practice and are a considerable economic burden. cIAIs are tissue-invasive infections leading to abscess formation or generalized peritonitis and requires surgical control of the source. Increasing resistance in pathogens that cause cIAI infections has lead to the need for new antimicrobials.
Eravacycline (ERV), an investigational agent not currently approved by the Food and Drug Administration, is an IV and oral broad-spectrum tetracycline antibiotic that is under clinical development by Tetraphase Pharmaceuticals for the treatment of serious infections, including those caused by multidrug-resistant Gram-negative and Gram-positive pathogens found in complicated intra- abdominal and urinary tract infections.
IGNITE1 was a Phase 3, randomized, double-blind, double-dummy, multicenter, prospective study to assess the efficacy, safety, and PK of eravacycline compared with ertapenem in adults with complicated intra-abdominal infections (cIAIs). Overall results from IGNITE1, have recently been reported. Certain high–risk patients are at greater risk of increased complications including a poor outcome with cIAI infections. Those patients are evaluated here.

Objective

The objective of this analysis is to compare outcomes between ERV and ETP in higher risk subgroups in patients with cIAI from IGNITE1.

Methods

Qualified subjects enrolled in the study were randomized to 1 of 2 treatment groups, eravacycline 1.0 mg/kg every 12 hours (q12h), or ertapenem 1 g every 24 hours (q24h), in a 1:1 ratio. Randomization was stratified based on the primary site of infection (complicated appendicitis versus all other diagnoses). Screening and baseline assessments were performed within 48 hours before the first dose of study drug. Subjects were evaluated on Day 1 through Day 14 and at the EOT Visit, which occurred within 24 hours of the last dose of the study drug; the TOC Visit, which occurred between Days 25 and 31; and at the Follow-up (FU) Visit, which occurred between Days 38 and 50. All subjects remained hospitalized for the complete course of drug therapy.

Methods (Cont)

Diagnosis and main criteria for inclusion: Subjects aged at least 18 years who:
• Were hospitalized for cIAI with a diagnosis of intra-abdominal abscess, gastric or intestinal perforation associated with diffuse peritonitis, peritonitis due to perforated viscus or other focus of infection, appendicitis, cholecystitis, intra-abdominal abscess (single or multiple; including hepatic and splenic abscesses), or peritonitis (local or diffuse)
- Had evidence of a systemic inflammatory response of fever, elevated white blood cell (WBC) count, increased pulse (heart rate), or increased respiratory rate
- Had abdominal pain or flank pain (with or without rebound tenderness), or pain caused by cIAI that was referred to another anatomic area such as back or hip, or localized or diffuse abdominal wall rigidity, or mass, or ileus
  - Had sonogram or radiographic imaging results congruent with the diagnosis of cIAI, and
  - Acute surgical or percutaneous intervention (open laparotomy, laparoscopic surgery, or percutaneous drainage of an abscess) was foreseen within 48 hours
- Or met intraoperative/postoperative criteria for enrollment:
  - Had visual confirmation of cIAI (presence of pus within the abdominal cavity), and
  - Surgical intervention included open laparotomy, laparoscopic surgery, or percutaneous draining of an abscess, and
  - Intervention was adequate (i.e., a procedure in which all communications between the gastrointestinal [GI] tract and the peritoneal cavity were closed, no necrotic intestine was left, and all infected collections were drained at the procedure)

Efficacy evaluation: This study was designed to demonstrate non-inferiority (NI) of eravacycline 1.0 mg/kg q12h to ertapenem 1.0 g q24h. The primary efficacy variable was the clinical response at the TOC visit in the micro-ITT population (US FDA) and in the MITT and CE populations (EMA). Clinical response was classified as cure, failure, or indeterminate based on clinical outcomes.
The secondary efficacy variables included:
- Clinical response in the following analysis populations at the EOT, TOC, and FU visits: ITT, MITT, micro-ITT, CE-EOT (or TOC) and ME-EOT (or TOC) populations
- Microbiological response at the EOT and TOC visits in the following analysis populations: micro-ITT population and ME population. Microbiological response categories were eradication, presumptive eradication, persistence, persistence with decreased susceptibility, presumed persistence, or assessment not possible. The categories were further classified as favorable (eradication, presumptive eradication), unfavorable (persistence, persistence with decreased susceptibility, presumed persistence), or indeterminate (assessment not possible).

Safety evaluation: All patients in the ITT population were evaluated for safety.

Results

Table 1: Baseline demographics of the patients in IGNITE1 in the micro-ITT population

	ERV N= 220	ETP N= 226
Gender, male, n%	126 (57.3)	132 (58.4)
Race, White, n%	214 (97.3)	215 (95.1)
Age, Mean, y (SD)		
<65	149 (67.7)	159 (70.4)
≥65 to 75	50 (22.7)	38 (16.8)
≥75	21 (9.5)	29 (12.8)
Body mass index, kg/m^2, mean (SD)	28.2 (5.8)	27.5 (5.0)
Baseline APACHE II category, n (%)		
<10	173 (78.6)	17 (77.0)
≥10	47 (21.4)	52 (23.0)
Presence of bacteremia	20 (9.1)	20 (8.8)
Diagnosed Intra/post-operatively, n (%)	198 (90.0)	189 (83.6)
Intra-abdominal abscess (es)	85 (42.9)	77 (40.7)
Complicated appendicitis	62 (31.3)	60 (31.7)
Perforation of intestine	26 (13.1)	33 (17.5)
Gastric/duodenal perforation	17 (8.6)	20 (10.6)
Peritonitis	62 (31.3)	65 (34.4)
Complicated cholecystitis	39 (19.7)	39 (20.6)
Other	10 (5.1)	4 (2.1)

Table 3: IGNITE1 Safety data in the ITT population

System Organ Class	ERV N= 270	ETP N= 268
Subjects with at least 1 TEAE	113 (41.9)	75 (28.0)
Gastrointestinal disorders	41 (15.2)	24 (9.0)
Nausea	22 (8.1)	2 (0.7)
Vomiting	11 (4.1)	9 (3.4)
Immune system disorders	2 (0.7)	0
Hypersensitivity	2 (0.7)	0
Infections and infestations	23 (8.5)	18 (6.7)
Postoperative wound infection	4 (1.5)	1 (0.4)
Wound infection	6 (2.2)	2 (0.7)
Injury, poisoning and procedural complications	16 (5.9)	6 (2.2)
Abdominal wound dehiscence	1 (0.4)	0
Wound dehiscence	5 (1.9)	1 (0.4)
Wound evisceration	1 (0.4)	0
Vascular disorders	22 (8.1)	7 (2.6)

ERV - eravacycline, ETP - ertapenem, SD - standard deviation,
TEAE - treatment emergent adverse event

Results

Table 2: Cure and failure rates in special populations in the micro-ITT population from IGNITE1

Group (N)	ERV Cure n (%)/Failure n (%)/Indeterminate n (%)	ETP Cure n (%)/Failure n (%)/Indeterminate n (%)	Difference in Clinical Cure 95% "CI (LL, UL)[1]
All (446)	191 (86.8)/ 19 (8.6)/ 10 (4.5)	198 (87.6)/ 11 (4.9)/ 17 (7.5)	-0.8 (-7.1, 5.5)
Age			
<65 (308)	132 (88.6)/ 9 (6.0) / 8 (5.4)	142 (89.3)/ 5 (3.1)/ 12 (7.6)	-0.7 (-8.0, 6.4)
≥65 to 75 (138)	59 (83.1)/ 10 (14.1)/ 2 (2.8)	56 (83.6)/ 6 (10.0)/ 5 7.5)	-0.5 (-13.0, 12.2)
≥75 (59)	26 (92.9)/ 2 (7.1)/ 0 (0.0)	28 (90.3)/ 2 (6.5)/ 1 (3.2)	2.5 (-14.2, 18.6)
Baseline APACHE II category			
<10 (347)	150 (86.7)/ 15 (8.7)/ 8 (4.6)	155 (89.1)/ 7 (4.0)/ 12 (6.9)	-2.4 (-9.4, 4.6)
≥10 (99)	41 (87.2)/ 4 (8.5)/ 2 (4.3)	43 (82.7)/ 4 (7.7)/ 5 (9.6)	4.5 (-10.2, 18.7)
Abscess (263)	120 (87.0)/ 12 (8.7)/ 6 (4.4)	108 (86.4)/ 8 (6.4)/ 9 (7.2)	0.6 (-7.7, 9.0)
Bacteremia at baseline (40)	17 (85.0)/ 1 (5.0)/ 2 (10.0)	15 (75.0)/ 1 (5.0)/ 4 (20.0)	10.0 (-15.2, 34.0)
Diagnosed Intra/post-operatively			
Intra-abdominal abscess (191)	77 (83.7)/ 9 (9.8)/ 6 (6.5)	84 (84.8)/ 8 (8.1)/ 7 (7.1)	-1.1 (-11.7, 9.2)
Perforation of intestine (67)	26 (83.9) /4 (12.9)/ 1 (3.2)	29 (80.6)/ 2 (5.6)/ 5 (13.0)	3.3 (-15.8, 21.3)
Gastric/duodenal perforation (46)	19 (95.0)/ 1 (5.0)/ 0 (0.0)	25 (96.2)/ 0 (0.0)/ 1 (3.9)	1.2 (-20.0, 14.4)
Peritonitis (152)	63 (88.7)/ 5 (7.0)/3 (4.2)	71 (87.7)/ 3 (3.7)/ 7 (8.6)	1.1 (-9.8, 11.5)
Complicated cholecystitis (85)	37 (88.1)/ 3 (7.1)/ 2 (4.8)	42 (97.7)/ 0 (0.0)/ 1 (2.3)	-9.6 (-22.8, 2.2)
Complicated appendicitis (133)	57 (85.1)/ 6 (9.0)/ 4 (6.0)	57 (86.4)/ 4 (6.1)/ 5 (7.6)	1.3 (-13.5, 10.9)
Other (16)	10 (91.0)/ 0 (0.0)/ 1 (9.1)	5 (100.0)/ 0 (0.0)/ 0 (0.0)	NR
Procedure type, n (%)			
Open (227)	112 (86.0)/ 14 (10.7)/ 5 (3.8)	126 (86.3)/10 (6.8)/ 10 (6.8)	-0.8, (-9.2, 7.42)
Laparoscopic (126)	56 (87.5)/ 4 (6.3)/ 4 (6.3)	56 (90.3)/ 1 (1.6)/ 5 (8.1)	-2.82 (-14.3, 8.7)
Percutaneous aspiration (41)	23 (92.0)/ 1 (4.0)/ 1 (4.0)	15 (93.8)/ 0 (0.0)/ 1 (6.3)	-1.75 (-19.5, 21.1)
Other	0	1 0.5)/ 0 (0.0)/ 1 (0.5)	NR

ERV- eravacycline, ETP- ertapenem
[1]Difference in Clinical cure- evaluated indeterminate as failures
NR- Not reported

Conclusions

- Outcomes in patients treated with ERV were similar to those treated with ETP in adults patients with cIAI among those with a higher risk of a poor outcome including advanced age, higher APACHE II score and presence of intra-abdominal abscess.
- No differences in outcomes were observed in patients treated with eravacycline between high-risk groups and the overall treatment population.
- Eravacycline may offer an alternative therapy in adult patients with cIAI, including patients at high risk for poor outcomes.