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Effect of Renal Function on Efficacy in IGNITE1: A Phase 3 Study to Evaluate the Efficacy and Safety of Eravacycline

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Abstract

Background: Abnormal renal function, whether impaired or augmented, is emerging as a risk factor for worse outcome in patients with serious bacterial infections. Eravacycline (ERV) is a novel fluorocycline that is highly active *in vitro* against multidrug-resistant bacterial pathogens encountered with increasing frequency in complicated intra-abdominal infections (cIAI). Overall results from IGNITE1, a phase 3 study to evaluate the efficacy and safety of ERV in the treatment of cIAI, have recently been reported. We sought to explore how baseline creatinine clearance (CL_{CR}) affects the clinical efficacy of ERV.

Methods: In this phase 3, randomized, double-blind, double-dummy, multicenter, prospective, phase 3 trial, patients with 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. Subjects were classified into 3 renal function categories based on baseline CL_{CR} calculated by the Cockcroft-Gault equation.

Results: 541 patients were randomized. The micro-ITT population consisted of 446 patients who grew at least one pathogen consistent with cIAI in baseline cultures. Clinical outcomes analyzed by categories of baseline renal function in the micro-ITT population at TOC were:

Group (N)	CL_{CR} (median [min, max])	ERV % Cure	ETP % Cure	Difference	95% CI (LL, UL)
All subjects (446)	107 [8, 266]	86.8	87.6	-0.8	(-7.1, 5.5)
Impaired Renal Function (43) [CL_{CR} <60 mL/min]	48 [8, 58]	79.2	73.7	5.5	(-18.9, 30.8)
Normal Renal Function (261) [CL_{CR} 60 to <130 mL/min]	94 [60, 129]	87.9	91.2	-3.3	(-11.2, 4.2)
Augmented (124) [CL_{CR} ≥130 mL/min]	153.5 [130, 266]	87.9	87.9	0.1	(-11.8, 12.2)

Conclusions: This study met its primary efficacy endpoint, demonstrating non-inferiority of ERV to ETP in the treatment of cIAI. ERV was effective in treating patients across the range of moderately-severely impaired to augmented renal function.
This study was registered with ClinicalTrials.gov (NCT01844856) and EudraCT (2013-001913-34) and was funded by Tetraphase Pharmaceuticals.

Introduction

Alterations of renal function are common in patients with critical illness, including serious bacterial infections. Impaired renal clearance may result from numerous factors, including systemic inflammation, shock, and nephrotoxic interventions. Augmented renal clearance, although increasingly recognized in critically ill patients, can be difficult to identify because serum creatinine often remains within the normal range. Either can have important implications for the accurate dosing of renally-eliminated medications, including anti bacterials, used in the treatment of these patients. In two recent studies of novel anti bacterials, adjustments for abnormal renal function may have resulted in under dosing and associated worse outcomes in some patients.

Eravacycline (ERV) is a novel fluorocycline that is highly active *in vitro* against multidrug-resistant bacterial pathogens encountered with increasing frequency in cIAI. Since eravacycline is cleared primarily through the hepatic route, alterations of renal function are not expected to significantly affect its pharmacokinetics or clinical efficacy.

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 cIAIs. Overall results from IGNITE1, have recently been reported.

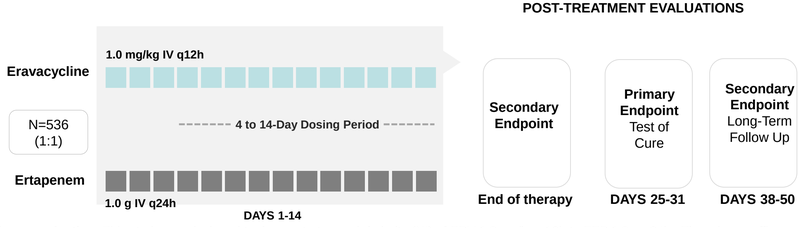
Methods

Qualified subjects enrolled in the study were randomized to 1 of 2 treatment groups, ERV 1.0 mg/kg IV every 12 hours (q12h), or ETP 1 g IV 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 end of treatment (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.

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
- And either met the criteria for preoperative enrollment:
  - 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)

Figure 1. IGNITE1 Clinical Trial Design – Overall and by Baseline Renal Function



Efficacy evaluation: This study was designed to demonstrate non-inferiority (NI) of ERV 1.0 mg/kg q12h to ETP 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 modified intent to treat (MITT) and clinically evaluable (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
  - Categories were further classified as favorable (eradication, presumptive eradication), unfavorable (persistence, persistence with decreased susceptibility, presumed persistence), or indeterminate (assessment not possible)
- Time to defervescence, defined as the time from the start of treatment with study drug until subject's temperature ≤37.6ºC and had a follow up temperature ≤37.6ºC within a 24-hr period

Analysis of renal function subgroups: Subjects were divided into 3 categories of renal function based upon their baseline creatinine clearance calculated by the Cockcroft-Gault equation (CL_{CR}) defined as follows: 1) impaired renal function = CL_{CR} <60 mL/min, 2) normal renal function = CL_{CR} 60 to <130 mL/min and 3) augmented renal function = CL_{CR} ≥130 mL/min. Clinical outcomes at the TOC visit and adverse events were analyzed for each renal function category.

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

Results

Table 1. IGNITE1 Demographics – Overall and by Baseline Renal Function in the micro-ITT population *

	Eravacycline				Ertapenem			
	All (n) (SD) N=214	CrCl >130mL/min N=66	CrCl 60-130 N=124	CrCl<60 N=24	All (n) (SD) N=213	CrCl >130Ll/min N=58	CrCl 60-130 N=137	CrCl<60 N=18
Mean Age (y) [SD]	55.1 (16.9)	41.7 (14.6)	58.6 (14.0)	73.8 (7.9)	55.7 (15.9)	45.2 (14.3)	58.0 (14.5)	72.3 (9.7)
Mean Wt (kg) [SD]	81.6[14.6]	87.7 [15.2]	79.2 [13.5]	77.3 [14.0]	80.9 [15.7]	87.0 [18.8]	78.5 [13.9]	79.4 [12.5]
Male (%)	123 (57.4)	41 (62.1)	70 (56.5)	12 (18.8)	124 (58.2)	35 (60.3)	81 (59.1)	8 (44.4)
Caucasian (%)	208 (97)	64 (97.0)	121 (97.6)	23 (95.8)	202 (94.8)	54 (93.1)	130 (94.9)	18 (100)
Apache Score (N)								
Mean [SD]	6.6 (4.2)	4.6 (3.3)	7.2 (4.5)	9.3 (2.4)	6.6 [3.8]	4.9 (3.3)	7.1 (3.8)	11.3 (3.0)
< 10 (%)	168 (78.5)	60 (90.9)	93 (75.0)	15 (62.5)	162 (76.1)	52 (89.7)	105 (76.6)	5 (27.8)
10-15 (%)	41 (19.1)	6 (9.1)	26 (21.0)	9 (37.5)	45 (21.1)	6 (10.3)	28 (20.4)	11 (61.1)
> 15 (%)	5 (2.3)	---	5 (4.0)	---	6 (2.2)	---	4 (2.9)	2 (11.1)
Complicated Appendicitis (CA) (%)	73 (27.0)	27 (40.9)	31 (25)	5 (20.8)	75 (27.7)	24 (41.4)	37 (27)	1 (5.5)
Other (%)	197 (73.0)	39 (59.1)	93 (75)	19 (79.2)	196 (72.3)	34 (58.6)	100 (73)	17 (94.5)

Table 2. IGNITE1 Efficacy – Overall and by Baseline Renal Function in the micro-ITT population

Group (N)	CL_{CR} (median [min, max])	ERV % Cure	ETP % Cure	% Difference	95% CI (LL, UL)
All subjects (446)*	107 [8, 266]	86.8	87.6	-0.8	(-7.1, 5.5)
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*There were 446 pts. who met the micro-ITT criteria for evaluation; however 427 had measured baseline, creatinine clearance

Table 3: IGNITE1 Safety data in the ITT population

System Organ Class	Eravacycline N= 270	Ertapenem 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)

Conclusions

- This study met its primary efficacy endpoint, demonstrating non-inferiority of ERV to ETP in the treatment of cIAI.
- There were no differences in clinical efficacy in any of the renal function strata evaluated.
- Eravacycline may offer and alternative therapy in adult patients with cIAI, including patients with abnormal renal function.