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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

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Eravacycline is a novel fluorocycline, highly active against Gram-positive and Gram-negative pathogens *in vitro*, including those with tetracycline and multidrug resistance. This phase 2, randomized, double-blind study was conducted to evaluate the efficacy and safety of two dose regimens of eravacycline compared with ertapenem in adult hospitalized patients with complicated intra-abdominal infections (cIAIs). Patients with confirmed cIAI requiring surgical or percutaneous intervention and antibacterial therapy were randomized (2:2:1) to receive eravacycline at 1.5 mg/kg of body weight every 24 h (q24h), eravacycline at 1.0 mg/kg every 12 h (q12h), or ertapenem at 1 g (q24h) for a minimum of 4 days and a maximum of 14 days. The primary efficacy endpoint was the clinical response in microbiologically evaluable (ME) patients at the test-of-cure (TOC) visit 10 to 14 days after the last dose of study drug therapy. Overall, 53 patients received eravacycline at 1.5 mg/kg q24h, 56 received eravacycline at 1.0 mg/kg q12h, and 30 received ertapenem. For the ME population, the clinical success rate at the TOC visit was 92.9% (39/42) in the group receiving eravacycline at 1.5 mg/kg q24h, 100% (41/41) in the group receiving eravacycline at 1.0 mg/kg q12h, and 92.3% (24/26) in the ertapenem group. The incidences of treatment-emergent adverse events were 35.8%, 28.6%, and 26.7%, respectively. Incidence rates of nausea and vomiting were low in both eravacycline groups. Both dose regimens of eravacycline were as efficacious as the comparator, ertapenem, in patients with cIAI and were well tolerated. These results support the continued development of eravacycline for the treatment of serious infections, including those caused by drug-resistant Gram-negative pathogens. (This study has been registered at ClinicalTrials.gov under registration no. NCT01265784.)

Complicated intra-abdominal infections (cIAIs) are infections that extend beyond the hollow viscus of origin into the peritoneal space and are associated with either abscess formation or peritonitis (1). The management of cIAIs involves surgical removal of tissue and/or percutaneous drainage in conjunction with the use of broad-spectrum antibiotics or antibiotic combinations. The selection of antimicrobial therapy must cover a complex flora composed of aerobic and anaerobic bacteria usually derived from the intestinal tract. Antibiotics used for the empirical treatment of community-acquired cIAIs should have activity against enteric Gram-negative anaerobic, facultative, and aerobic bacilli and Gram-positive aerobic and anaerobic rods and cocci.

The increasing incidence of multidrug resistance among Gram-positive and Gram-negative pathogens has raised concerns among experts (2). One of the most common resistance mechanisms is the production of extended-spectrum β-lactamases (ESBLs) (3). Carbapenems are currently the treatment of choice for serious infections caused by ESBL-producing organisms, yet the frequency of carbapenem-resistant isolates is increasing. These strains are recognized in health care settings as a cause of difficult-to-treat infections associated with high mortality and morbidity (3–7).

Eravacycline (formerly TP-434) is a novel, fully synthetic antibiotic of the tetracycline class (8). Eravacycline was designed to be active against the two main acquired tetracycline-specific resistance mechanisms, ribosomal protection and active drug efflux (9, 10). In *in vitro* studies, the compound has shown potent activity against a broad spectrum of susceptible and multidrug-resistant bacteria, including Gram-negative, Gram-positive, and anaerobic bacteria (11). Eravacycline has a potency profile similar to that of carbapenems except that it more broadly covers Gram-positive pathogens, like methicillin-resistant *Staphylococcus aureus* and enterococci, is active against carbapenem-resistant Gram-negative bacteria, but is not active against *Pseudomonas aeruginosa* (8).

The objective of the current study (registration no. NCT01265784) was to evaluate the efficacy, safety, and pharmacokinetics of two dose regimens of eravacycline versus ertapenem in the treatment of cIAIs in hospitalized adults. The results of the pharmacokinetic analyses will be reported separately.

MATERIALS AND METHODS

This phase 2, randomized, double-blind, active-control study was performed in accordance with International Conference on Harmonization/Good Clinical Practice guidelines and applicable regulatory requirements. Patients were enrolled at 19 sites in six countries (United States, Bulgaria, Lithuania, Latvia, Romania, and India). The study protocol was approved

Received 1 August 2013 Returned for modification 20 September 2013
Accepted 8 December 2013
Published ahead of print 16 December 2013
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doi:10.1128/AAC.01614-13
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by each institutional review board, and each patient provided written informed consent.

Study population. Male and female patients, 18 to 75 years of age, with a body mass index of ≤30 kg/m^2 and a diagnosis of cIAI requiring urgent surgical or percutaneous intervention and not expected to require antibacterial therapy for longer than 14 days (7 days for patients in India) were eligible for inclusion. For preoperative enrollment, patients were required to have a sonogram or radiographic imaging results congruent with the diagnosis of cIAI; acute surgical or percutaneous intervention was foreseen; it was planned to have a specimen collected by aspiration or a tissue sample sent for culture and sensitivity; and they met the clinical diagnosis of cIAI. For intraoperative or postoperative enrollment, patients had visual confirmation of pus within the abdominal cavity, had samples for aerobic and anaerobic culture taken by aspiration or a tissue sample, and had surgical intervention in which the initial intervention was considered adequate. The acceptable diagnoses were as follows: appendiceal perforation and periappendiceal abscess, diverticulitis abscess, acute gastric and duodenal perforation if operated on >24 h after the perforation, traumatic perforation of the intestines if operated on >12 h after the perforation, and/or abscess or peritonitis due to perforated viscus or another focus of infection or other intra-abdominal abscess excluding liver and spleen from a gastrointestinal source.

Major exclusion criteria included the following: symptoms related to diagnosis of complicated appendicitis for <24 h prior to the current hospitalization, previous hospitalization within 6 months of screening, management by staged abdominal repair or other open abdominal technique, Acute Physiology and Chronic Health Evaluation (APACHE) II score of >25, anticipated survival less than the study period, rapidly progressing disease or immediately life-threatening illness, requirement for vasopressors at therapeutic dosages to maintain a systolic blood pressure of ≥90 mm Hg or diastolic blood pressure of ≥70 mm Hg, renal failure or abnormal renal function, abnormal liver function, or known or suspected inflammatory bowel disease or associated visceral abscess. Patients were also excluded if they had received systemic antibiotics for the current condition for >24 h, received ertapenem or any other carbapenem or tigecycline for the current infection, or required systemic antimicrobial agents other than a study drug.

Eligible patients were randomized in a 2:2:1 ratio to receive an intravenous (i.v.) infusion of eravacycline at 1.5 mg/kg of body weight every 24 h (q24h), eravacycline at 1.0 mg/kg every 12 h (q12h), or ertapenem at 1 g (q24h). Randomization was stratified based on the primary site of infection (complicated appendicitis versus all other diagnoses). An enrollment cap of 50% for patients with complicated appendicitis was planned.

Investigators and patients were blinded to the i.v. study antibiotic regimen. The study site's unblinded pharmacist obtained each patient's study identification number and study drug assignment from a computer-generated randomization coding scheme using an interactive web-based response system and prepared the solutions for infusion. To maintain blinding, matching placebo infusions were used and infusions and infusion lines were masked. The unblinded pharmacist provided the investigator with ready-to-use blinded infusion solutions for administration at scheduled study drug infusion times.

Patients were hospitalized while receiving the study drug. Eravacycline was administered intravenously over 60 min, while ertapenem was administered intravenously over 30 min. Due to differences between eravacycline and ertapenem infusion volumes, the timing of study drug administration (q12h versus q24h), and the length of infusion time (30 min versus 60 min), the study used a double-dummy methodology. During each 24-h period of study drug administration, the patient received three infusions.

Patients were treated for a minimum of 4 days and a maximum of 14 days, depending on clinical response. No other concomitant systemic antibiotics were permitted. Patients who required concomitant systemic antibiotics were withdrawn from the study drug and considered treatment failures. Test-of-cure (TOC) evaluations occurred 10 to 14 days after the last dose of the study drug. A follow-up visit occurred 28 to 42 days after the last dose of the study drug.

Assessments. Clinical outcome assessments included abdominal examination, surgical wound assessment (if applicable), and other pertinent examinations and were performed at the end-of-treatment (EOT), TOC, and follow-up visits. Samples from the site of intra-abdominal infection for culture and susceptibility testing were obtained at the time of the initial surgical procedure, at subsequent reinterventions, and if there were any signs and symptoms at the EOT, TOC, and follow-up visits. Other cultures were obtained during the study as clinically indicated. Blood cultures were taken if the patient had clinical signs of bacteremia.

Safety assessments included adverse events, laboratory tests, vital signs, electrocardiograms, and physical examinations. Treatment-emergent adverse events (TEAEs) were defined as adverse events that started during or after the first dose of study drug administration or increased in severity or relationship to the study drugs during the study. Serious adverse events (SAEs) were defined as those that resulted in death, were life-threatening, required hospitalization or prolonged existing hospitalization, resulted in persistent or significant disability or incapacity, were a congenital anomaly or birth defect, or were considered to be an important medical event.

Statistical methodology. The primary efficacy endpoint was the clinical response at the TOC visit in the microbiologically evaluable (ME) population, a subset of the clinically evaluable (CE) population. The CE population included all randomized patients who received any amount of a study drug and met the minimal disease definition of cIAI and for whom sufficient information was available to determine outcome with no confounding factors present that interfered with assessment of outcome. The ME population included CE patients who also had a baseline pathogen identified and a microbiological response assessed. Clinical response was classified as cure, failure, or indeterminate based on clinical outcomes. A favorable clinical response was cure, defined as complete resolution or significant improvement of signs and symptoms of the initial infection such that no additional antibacterial therapy or surgical or radiological intervention was required. Patients were classified as clinical failures based on death related to intra-abdominal infection, persisting or recurrent infection within the abdomen documented by findings at reintervention, postsurgical wound infection, or administration of effective concomitant antibacterial therapy for any indication after the start of study drug. Clinical response was also evaluated at the EOT and follow-up visits.

Clinical response rates with the associated 95% confidence intervals (CIs) using the Clopper-Pearson method (12) were calculated for each treatment group and each randomization stratum (primary site of infection). The continuity-corrected exact 95% CIs for the difference in clinical response rates between treatment groups (13) were also calculated.

Per-pathogen and per-patient microbiological responses were evaluated at the EOT and TOC visits in the microbiologically modified intent-to-treat (m-MITT) and ME populations. The m-MITT population included all randomized patients who received any amount of a study drug, met the minimal disease definition of cIAI, and had a baseline pathogen identified, regardless of susceptibility to the study drug. MIC determinations were made according to CLSI methods (23). Per-pathogen microbiological response categories were eradication, presumed eradication, persistence, presumed persistence, or assessment not possible. The categories were further classified as favorable (eradication or presumed eradication), unfavorable (persistence or presumed persistence), or indeterminate (assessment not possible). Per-patient microbiological response categories were eradication, presumed eradication, persistence, presumed persistence, superinfection, recurrent infection, entry culture not obtained, no baseline pathogen identified, or unknown.

Per-pathogen and per-patient microbiological response rates with the associated 95% CIs were calculated for each treatment group. The number of favorable responses was determined for each pathogen at each MIC level available for that pathogen. Data were summarized for each individual pathogen and the broad pathogen types for both the EOT and TOC visits.

TABLE 1 Study disposition for the intent-to-treat population

Parameter	Value for group, *n* (%)		
	Eravacycline at 1.5 mg/kg q24h	Eravacycline at 1.0 mg/kg q12h	Ertapenem at 1 g q24h
Randomized	56	57	30
Complicated appendicitis stratum	30	31	15
Other diagnosis stratum	26	26	14
Missing stratum	0	0	1
Completed study drug treatment[a]	52 (93)	53 (93)	27 (90)
Discontinued study drug[a]	2 (4)	3 (5)	2 (7)
Adverse event	2 (4)	0	2 (7)
Duodenal ulcer hemorrhage	1 (2)	0	0
Atrial fibrillation	1 (2)	0	0
Allerigic reaction	0	0	2 (7)
Withdrawal of consent	0	3 (5)	0
Completed study[a,b]	44 (79)	49 (86)	26 (87)
Did not complete the study[a,b]	10 (18)	7 (12)	3 (10)
Lost to follow-up	5 (9)	3 (5)	2 (7)
Withdrawal of consent	0	4 (7)	0
Physician decision	1 (2)	0	1 (3)
Other	4 (7)	0	0
Randomized but never dosed	2 (4)		
Fatal thromboembolism	1 (2)		
Not available for follow-up visit	1 (2)		

[a] Percentages are based on the number of randomized patients.
[b] Study completion was defined as completion of the follow-up visit.

TABLE 2 Analysis populations[a]

Population	Value for group, *n* (%)		
	Eravacycline at 1.5 mg/kg q24h	Eravacycline at 1.0 mg/kg q12h	Ertapenem at 1 g q24h
ITT[b]	56 (100)	57 (100)	30 (100)
MITT[c]	54 (96)	56 (98)	29 (97)
m-MITT[d]	45 (80)	47 (82)	27 (90)
CE[e]	49 (88)	48 (84)	28 (93)
ME[f]	42 (75)	41 (72)	26 (87)
Safety[g]	54 (96)	56 (98)	29 (97)

[a] Percentages are based on the ITT population. One patient was randomized to eravacycline at 1.5 mg/kg q24h but received ertapenem. ITT, intent-to-treat; MITT, modified intent-to-treat; m-MITT, microbiologically modified intent-to-treat.
[b] The ITT population included all randomized patients.
[c] The MITT population included all ITT patients who received any amount of study drug.
[d] The m-MITT population included all MITT patients who met the minimal disease definition of cIAI and had a baseline pathogen identified.
[e] The CE population included all MITT patients who met the minimal disease definition of cIAI and had a clinical response assessed at the test-of-cure visit.
[f] The ME population included all CE patients who had a baseline pathogen identified and a microbiological response assessed.
[g] The safety population included all randomized patients who received any amount of study drug.

An exploratory efficacy endpoint was time to defervescence, defined as the first time after the start of study drug treatment that a patient's temperature was ≤38°C and remained ≤38°C for all evaluations over the following 24-h period. Patients who discontinued treatment with the study drug prior to attaining defervescence were censored at the last evaluation at which the temperature was >38°C. Time to defervescence was displayed graphically using Kaplan-Meier methodology (14). The Wilcoxon test (15) was used for pairwise comparisons of the Kaplan-Meier curves between treatment groups.

The safety population included all randomized patients who received any amount of study drug. Patients were evaluated as treated. The number and percentage of patients who experienced TEAEs and SAEs were summarized by system organ class and preferred term levels using the *Medical Dictionary for Regulatory Activities* (MedDRA) (16) and tabulated by treatment group.

This study was not statistically powered to demonstrate noninferiority of either eravacycline treatment group to the comparator, ertapenem, but was intended to provide an estimate of efficacy and safety. Approximately 150 randomized patients were expected to provide at least 115 patients (46 in each of the eravacycline groups and 23 in the ertapenem group) in the ME population.

RESULTS

The study was conducted from January 2011 to May 2012. In total, 143 patients were assigned randomly to receive study drug treatment: eravacycline at 1.5 mg/kg q24h (56 patients), eravacycline at 1.0 mg/kg q12h (57 patients), and ertapenem at 1 g q24h (30 patients). Four patients did not receive a study drug. One patient was assigned to receive eravacycline at 1.5 mg/kg but received ertapenem. Overall, 53 patients received eravacycline at 1.5 mg/kg q24h, 56 received eravacycline at 1.0 mg/kg q12h, and 30 received ertapenem. The numbers of patients in each treatment group who completed study drug treatment were 52, 53, and 27, respectively (Table 1). More than 80% of patients in each treatment group completed the study through the follow-up visit.

Exposures to study drug treatment were similar for the treatment groups. The median durations of treatment were 6.7, 6.3, and 6.2 days for patients in the groups receiving eravacycline at 1.5 mg/kg, eravacycline at 1.0 mg/kg, and ertapenem, respectively.

Analysis populations. The m-MITT population comprised 45 patients in the group receiving eravacycline at 1.5 mg/kg, 47 patients in the group receiving eravacycline at 1.0 mg/kg, and 27 patients in the ertapenem group (Table 2). One patient in the ertapenem group did not meet the minimal cIAI definition. No baseline pathogen was identified in 22 patients (10, 9, and 3 in each group, respectively).

The CE population comprised 49 patients in the group receiving eravacycline at 1.5 mg/kg, 48 patients in the group receiving eravacycline at 1.0 mg/kg, and 28 patients in the ertapenem group. The ME population, a subset of the CE population, included 42 patients in the group receiving eravacycline at 1.5 mg/kg, 41 patients in the group receiving eravacycline at 1.0 mg/kg, and 26 patients in the ertapenem group.

Demographic and baseline characteristics. Patients were primarily male (72.0%) and Caucasian (68.5%), with a mean age of 41.8 years (Table 3). The mean APACHE II score was 6.9. For the MITT population, 54% of patients had complicated appendicitis and 46% of patients had ≥1 other diagnosis. Demographic and baseline characteristics, including the primary site of infection, were similar for the treatment groups.

***In vitro* susceptibility of baseline cultures.** In total, 119 patients had an intra-abdominal pathogen identified at baseline. The majority of baseline pathogens identified were Gram-negative aerobes (67.9%), followed by Gram-positive aerobes (23.6%), Gram-negative anaerobes (5.7%), and Gram-positive anaerobes (2.8%). *Escherichia coli* (60.3%) was the most common Gram-negative pathogen. *Enterococcus faecalis* (6.7%) was the most common Gram-positive aerobe, and *Bacteroides fragilis* (5.0%) was the most common Gram-negative anaerobe.

For the ME population, 191 isolates were identified in baseline

TABLE 3 Demographic and baseline characteristics for the intent-to-treat population

Parameter	Value for group		
	Eravacycline at 1.5 mg/kg q24h ($n = 56$)	Eravacycline at 1.0 mg/kg q12h ($n = 57$)	Ertapenem at 1 g q24h ($n = 30$)
Gender, *n* (%)			
Male	38 (67.9)	43 (75.4)	22 (73.3)
Female	18 (32.1)	14 (24.6)	8 (26.7)
Race, *n* (%)			
Caucasian	40 (71.4)	37 (64.9)	21 (70.0)
Asian	16 (28.6)	20 (35.1)	9 (30.0)
Age (yrs), mean (SD)	43.6 (18.4)	42.1 (17.2)	41.8 (17.6)
Body mass index (kg/m^2), mean (SD)	23.3 (3.5)	23.6 (3.8)	23.4 (3.8)
APACHE II score, mean (SD)	8.2 (3.9)	6.0 (3.8)	6.1 (2.7)
Site of infection, *n* (%)[a]			
Complicated appendicitis	29 (53.7)	31 (55.4)	15 (51.7)
Other	25 (46.3)	25 (44.6)	14 (48.3)
Peritonitis	13 (24.1)	14 (25.0)	7 (24.1)
Gastric/duodenal perforation	13 (24.1)	12 (21.4)	8 (27.6)
Intestinal perforation	5 (9.3)	4 (7.1)	1 (3.4)
Complicated cholecystitis	3 (5.6)	4 (7.1)	3 (10.3)
Intra-abdominal abscess	1 (1.9)	2 (3.6)	1 (3.4)
Complicated diverticulitis	0	2 (3.6)	0
Other	0	1 (1.8)	1 (3.4)

[a] Numbers and percentages are based on the modified intent-to-treat population.

cultures from 109 patients (Table 4). Two or more distinct isolates were identified in baseline cultures from 52.4% (22/42) of patients in the group receiving eravacycline at 1.5 mg/kg, 41.5% (17/41) of patients in the group receiving eravacycline at 1.0 mg/kg, and 46.2% (12/26) of patients in the ertapenem group. The highest MIC for eravacycline was for *Pseudomonas aeruginosa*, with a range of 4 to 16 μg/ml; the corresponding MIC range for ertapenem was 1 to 32 μg/ml. Excluding *P. aeruginosa*, the highest MIC for eravacycline was 2 μg/ml for at least one of the *Klebsiella pneumoniae* isolates.

Clinical response. For the ME population, the clinical success rates at the TOC visit were 92.9% (39/42) in the group receiving eravacycline at 1.5 mg/kg, 100% (41/41) in the group receiving eravacycline at 1.0 mg/kg, and 92.3% (24/26) in the ertapenem group (Table 5). The estimated difference in clinical success rates between eravacycline at 1.5 mg/kg and ertapenem was 0.5% (95% CIs, −23.1%, 25.2%). The estimated difference in clinical success rates between eravacycline at 1.0 mg/kg and ertapenem was 7.7% (95% CIs, −6.7%, 40.9%). Reasons for clinical failure for the 3 patients in the group receiving eravacycline at 1.5 mg/kg were persistent fever at EOT for 1 patient (baseline pathogens, *Klebsiella pneumoniae* [2 strains] and *Pseudomanas aeruginosa* [2 strains]) and lobar pneumonia after EOT for 1 patient (baseline pathogen, *Gemella morbillorum*), both events which required treatment with other antibiotics, and fatal thromboembolism at EOT for 1 patient (baseline pathogen, *Escherichia coli*) (Table 6). Reasons for clinical failure for the 2 patients in the ertapenem group were a new subphrenic abscess that resulted in a repeat abdominal procedure for 1 patient (baseline pathogens, *Klebsiella pneumoniae*, *Acinetobacter* spp., and *Streptococcus salivarius* [2 strains]) and an allergic reaction for 1 patient (baseline pathogens, *Bacteroides fragilis* and *Escherichia coli*) that required other antibiotic treatment.

TABLE 4 *In vitro* susceptibility testing results of baseline pathogens for intra-abdominal isolates for the microbiologically evaluable population

Organism(s)	Total	MIC (μg/ml) for eravacycline			MIC (μg/ml) for ertapenem		
		Range	50%	90%	Range	50%	90%
Gram-positive aerobic pathogens	45	0.008, 0.12	0.03	0.06	0.015, 32	0.5	16
Enterococcus avium	2	0.015, 0.03			8, 8		
Enterococcus faecalis	7	0.03, 0.06	0.06	0.06	1, 32	4	32
Enterococcus faecium	3	0.03, 0.06	0.06	0.06	2, 32	16	32
Staphylococcus aureus	6	0.03, 0.12	0.06	0.12	0.06, 1	0.12	1
Staphylococcus epidermidis	2	0.03, 0.06			0.06, 0.5		
Streptococcus agalactiae	2	0.03, 0.03			0.06, 0.06		
Streptococcus anginosus	4	0.008, 0.03	0.015	0.03	0.12, 0.25	0.12	0.25
Streptococcus bovis	2	0.015, 0.03			0.03, 0.06		
Streptococcus mitis	2	0.008, 0.03			0.03, 0.06		
Streptococcus salivarius	3	0.015, 0.06	0.015	0.06	0.03, 1	0.03	1
Gram-negative aerobic pathogens	129	0.015, 16	0.25	1	0.002, 32	0.004	2
Acinetobacter baumannii complex	4	0.25, 0.5	0.5	0.5	32, 32	32	32
Comamonas testosteroni	2	0.015, 0.03			0.002, 0.004		
Escherichia coli	86	0.12, 1	0.25	0.5	0.002, 32	0.004	0.12
Klebsiella oxytoca	6	0.25, 1	0.5	1	0.004, 0.008	0.008	0.008
Klebsiella pneumoniae	14	0.25, 2	0.5	1	0.002, 16	0.008	0.06
Morganella morganii	3	1, 1	1	1	0.008, 0.008	0.008	0.008
Proteus mirabilis	2	0.5, 1			0.008, 0.008		
Pseudomonas aeruginosa	6	4, 16	16	16	1, 32	16	32
Gram-positive anaerobic pathogens	6	0.06, 0.5	0.06	0.5	0.12, 2	0.12	2
Gram-negative anaerobic pathogens	11	0.06, 1	0.12	1	0.25, 4	0.25	4
Bacteroides fragilis	4	0.06, 1	0.25	1	0.25, 4	0.25	4
Bacteroides ureolyticus	3						
Bacteroides vulgatus	2	0.12, 0.12			0.25, 1		

TABLE 5 Clinical response at the TOC visit overall and by baseline infection stratum for the microbiologically evaluable population

Parameter	Value (%) for group		
	Eravacycline at 1.5 mg/kg q24h ($n = 42$)	Eravacycline at 1.0 mg/kg q12h ($n = 41$)	Ertapenem at 1 g q24h ($n = 26$)
Overall			
Cure rate	39/42 (92.9)	41/41 (100)	24/26 (92.3)
Failure rate	3/42 (7.1)	0/41	2/26 (7.7)
95% CI on the cure rate	80.5, 98.5	91.4, 100	74.9, 99.1
Complicated appendicitis			
Cure rate	26/27 (96.3)	24/24 (100)	12/13 (92.3)
Failure rate	1/27 (3.7)	0/24	1/13 (7.7)
95% CI on the cure rate	81.0, 99.9	85.8, 100	64.0, 99.8
Other diagnosis			
Cure rate	13/15 (86.7)	17/17 (100)	12/13 (92.3)
Failure rate	2/15 (13.3)[a]	0/17	1/13 (7.7)[b]
95% CI on the cure rate	59.5, 98.3	80.5, 100	64.0, 99.8

[a] One subject presented with peritonitis and one subject presented with intestinal perforation.
[b] Subject presented with gastric/duodenal perforation.

TABLE 7 Microbiological response by visit for the microbiologically evaluable population

Response	Value (%) for group		
	Eravacycline 1.5 mg/kg q24h ($n = 42$)	Eravacycline 1.0 mg/kg q12h ($n = 41$)	Ertapenem 1 g q24h ($n = 26$)
EOT visit			
Favorable	40/42 (95.2)	41/41 (100)	25/26 (96.2)
Unfavorable	2/42 (4.8)	0/41	1/26 (3.8)
95% CI on the favorable rate	83.8, 99.4	91.4, 100	80.4, 99.9
TOC visit			
Favorable	39/42 (92.9)	41/41 (100)	24/26 (92.3)
Unfavorable	3/42 (7.1)	0/41	2/26 (7.7)
95% CI on the favorable rate	80.5, 98.5	91.4, 100	74.9, 99.1
Follow-up visit			
Favorable	37/42 (88.1)	40/41 (97.6)	23/26 (88.5)
Unfavorable	4/42 (9.5)	0/41	2/26 (7.7)
Indeterminate	1/42 (2.4)	1/41 (2.4)	1/26 (3.8)
95% CI on the favorable rate	74.4, 96.0	87.1, 99.9	69.8, 97.6

Clinical response results from patients stratified by complicated appendicitis and other diagnoses were consistent with the overall results. Similar clinical response results were observed at the EOT and follow-up visits for the ME population (Table 5) and at the TOC, EOT, and follow-up visits for the other analysis populations.

For the m-MITT population, 28 (23.5%) patients produced 36 of 144 (25.0%) Gram-negative isolates that were ESBL producers, as defined as intermediate or resistant to ceftazidime and/or cefotaxime by Clinical and Laboratory Standards Institute guidelines (15). If no breakpoint for a species was given, then the organism was presumed resistant. For the subgroup of patients with ESBL-producing pathogens, the clinical success rates at TOC were 80.0% (8/10) in the group receiving eravacycline at 1.5 mg/kg, 100% (10/10) in the group receiving eravacycline at 1.0 mg/kg, and 100% (4/4) in the ertapenem group.

Microbiological outcomes. For the ME population, the percentage of patients in the eravacycline groups with a favorable (eradicated or presumed eradicated) microbiological response was comparable to that of the ertapenem group at each visit (Table 7). At the EOT visit, favorable microbiological responses were observed in 95.2% (40/42) of patients in the group receiving eravacycline at 1.5 mg/kg, 100% (41/41) of patients in the group receiving eravacycline at 1.0 mg/kg, and 96.2% (25/26) of patients in the ertapenem group. At the TOC visit, the favorable microbiological response rates were 92.9% (39/42), 41/41 (100%), and 92.3% (24/26), respectively. At the follow-up visit, the favorable microbiological response rates were 88.1% (37/42), 97.6% (40/41), and 88.5% (23/26), respectively. The microbiological response rates for the m-MITT population were consistent with those for the ME population.

The per-pathogen microbiological response rates were consistent with the relative percentage of patients in each treatment group with an eradicated or presumed eradicated response. At the EOT visit, most baseline pathogens had a microbiological response of favorable and presumed eradicated and remained favorable and presumed eradicated at the TOC and follow-up visits for the three treatment groups. The pathogens with an unfavorable microbiological response at EOT for ≥1 patients in the ME population were *Escherichia coli* (1 patient in the group receiving eravacycline at 1.5 mg/kg and 1 patient in the ertapenem group), *Klebsiella pneumoniae* (1 patient in the group receiving eravacycline at 1.5 mg/kg), *Pseudomonas aeruginosa* (1 patient in the group receiving eravacycline at 1.5 mg/kg), *Gemella morbillorum* (1 patient in the group receiving eravacycline at 1.5 mg/kg), and *Bacteroides fragilis* (1 patient in the ertapenem group).

Time to defervescence. For the MITT population, the percentages of patients who achieved defervescence were 88.9% for the group receiving eravacycline at 1.5 mg/kg, 96.4% for the group receiving eravacycline at 1.0 mg/kg, and 100% for the ertapenem group. The estimated median time to defervescence was lowest for the group receiving eravacycline at 1.0 mg/kg (15.7 h), followed by the ertapenem group (31.3 h) and the group receiving eravacycline at 1.5 mg/kg (60.0 h). Figure 1 displays the Kaplan-Meier curves for time to defervescence for the three treatment groups. The comparisons of each of the eravacycline groups with ertapenem for time to defervescence were not statistically significant.

Safety and tolerability. The percentages of patients who had at

TABLE 6 Reasons for clinical failure at the TOC visit for the microbiologically evaluable population

Reason for clinical failure	No. of patients	
	Eravacycline at 1.5 mg/kg q24h	Ertapenem at 1 g q24h
Persistent/recurrent intra-abdominal infection	1 (persistent fever)	1 (new abscess)
Adverse event related	1 (thrombosis)	1 (hypersensitivity)
Remote site infection	1 (pneumonia)	
Total	3	2

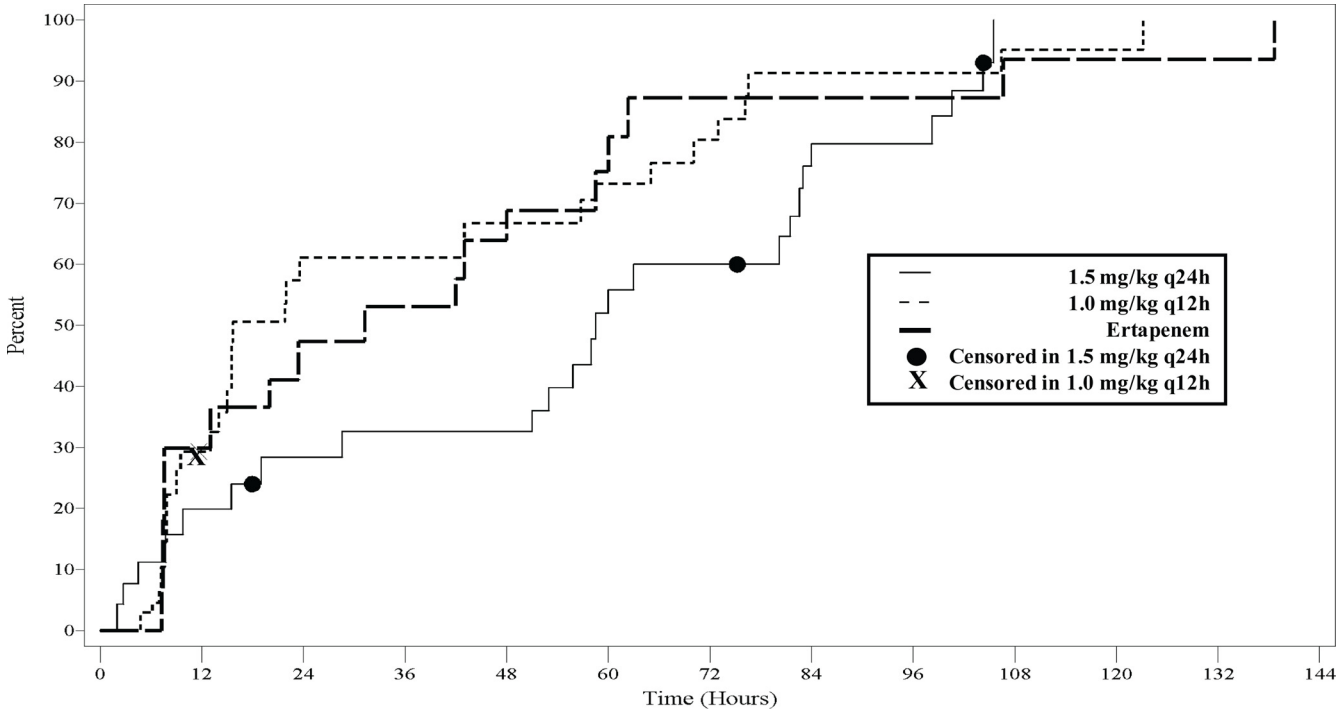

FIG 1 Kaplan-Meier probability plot of time to defervescence (hours) in the modified intent-to-treat population.

least 1 TEAE during the study were 35.8% (19/53) in the group receiving eravacycline at 1.5 mg/kg, 28.6% (16/56) in the group receiving eravacycline at 1.0 mg/kg, and 26.7% (8/30) in the ertapenem group. The most common TEAEs were gastrointestinal in nature, including nausea (1.9% for eravacycline at 1.5 mg/kg, 10.7% for eravacycline at 1.0 mg/kg, and 6.7% for ertapenem) and vomiting (5.7%, 1.8%, and 0%, respectively) (Table 8). Most TEAEs were mild in severity and considered by the investigator to be unrelated to the study drug.

Two patients in the group receiving eravacycline at 1.5 mg/kg and 2 patients in the ertapenem group had a TEAE that resulted in discontinuation of study drug treatment. Six patients in the group receiving eravacycline at 1.5 mg/kg, 1 patient in the group receiving eravacycline at 1.0 mg/kg, and 1 patient in the ertapenem group had an SAE during the study, none of which was considered by the investigator to be related to the study drug. Among the SAEs were 3 deaths in the group receiving eravacycline at 1.5 mg/kg (duodenal ulcer hemorrhage for 1 patient on day 2 of therapy, atrial fibrillation for 1 patient on day 4 of therapy, and embolism for 1 patient on the first day following completion of therapy).

No safety signals as evaluated by laboratory tests, physical examinations, vital sign measurements, or electrocardiograms were identified.

TABLE 8 Summary of treatment-emergent adverse events occurring in >1 patient in any treatment group for the safety population

Adverse event	Value (%) for group		
	Eravacycline at 1.5 mg/kg q24h ($n = 53$)	Eravacycline at 1.0 mg/kg q12h ($n = 56$)	Ertapenem at 1 g q24h ($n = 30$)
Any TEAE	19 (35.8)	16 (28.6)	8 (26.7)
Abdominal pain	2 (3.8)	0	0
Ileus	2 (3.8)	0	0
Nausea	1 (1.9)	6 (10.7)	2 (6.7)
Vomiting	3 (5.7)	1 (1.8)	0
Blood amylase increased	3 (5.7)	2 (3.6)	1 (3.3)
Lipase increased	3 (5.7)	4 (7.1)	2 (6.7)
Thrombophlebitis	1 (1.9)	2 (3.6)	0

DISCUSSION

This phase 2, randomized, double-blind study compared two dose regimens of eravacycline with ertapenem, a carbapenem antibiotic with demonstrated effectiveness in cIAI (17–19) and a recommended first-line empirical monotherapy for the treatment of community-acquired cIAIs (1). Eravacycline, at both dose regimens of 1.5 mg/kg q24h and 1.0 mg/kg q12h, had efficacy comparable to that of ertapenem on clinical and microbiological endpoints. Eravacycline was generally well tolerated and had a safety and tolerability profile similar to that of the comparator agent.

Similar favorable response rates of >90% were observed in all three treatment groups for the primary efficacy endpoint of clinical response at the TOC visit in the ME population. For patients treated with eravacycline at 1.0 mg/kg, the clinical cure rate at TOC was 100%. The high clinical cure rates were also seen in subgroup analyses that evaluated patients with either complicated appendicitis or cIAI resulting from other conditions. The response rates were also comparable to that of ertapenem at the end of i.v. therapy and at the follow-up visit in the ME population. Analyses of clinical response on other patient populations confirmed the primary efficacy results.

These findings of clinical success extended to other clinical efficacy endpoints. The time to defervescence, although not statis-

tically different for eravacycline from ertapenem, was lowest for patients treated with eravacycline at 1.0 mg/kg. Furthermore, the length of study drug treatment was approximately 6 days for all three treatment groups.

Similar favorable (eradication and presumed eradication) microbiological response rates were observed in the three treatment groups at the EOT, TOC, and follow-up visits for the ME and m-MITT populations. Favorable microbiological response rates were >95% in all treatment groups at EOT for the ME population. Eravacycline demonstrated a high response rate against a wide variety of multidrug-resistant Gram-negative, Gram-positive, and anaerobic bacteria. Of particular note, in the combined eravacycline groups, 90% (18/20) of patients with ESBL-producing Gram-negative pathogens had a clinical response of cure at TOC (100% cure rate for patients treated with eravacycline at 1.0 mg/kg).

In this study, the most common baseline pathogens were *Escherichia coli*, *Klebsiella* spp., streptococci, enterococci, and *Bacteroides* spp., consistent with those associated typically with cIAI, although the recovery of anaerobic pathogens was lower in the present study than in some recent reports (20, 21). These pathogens were eradicated at similar rates by both study drugs. The per-pathogen microbiological response rates are supported by a review of the MICs for the 191 baseline pathogens isolated in the ME population. Excluding *P. aeruginosa* and *K. pneumoniae*, all pathogens had an MIC for eravacycline of ≤1 μg/ml; the majority were much lower. The MICs from isolates of this clinical trial support the previous *in vitro* results obtained with eravacycline and demonstrate the broad spectrum of the antimicrobial activity of eravacycline. For comparison, isolates from 11 species had MICs for ertapenem that were ≥2 μg/ml.

No safety signals were identified in this study. No patient had an SAE that was considered related to the study drugs. Fewer than 40% of patients in any treatment group experienced a TEAE, and overall adverse event rates were similar for patients treated with eravacycline and for patients treated with ertapenem. Tigecycline has been associated with dose-limiting nausea and vomiting (22). In this study, the incidence rates of gastrointestinal adverse events such as nausea and vomiting in the eravacycline groups were low and comparable to the rates of such events in the ertapenem group. None of the gastrointestinal adverse events led to discontinuation of study drug treatment.

Potential limitations of this study include the planned inclusion of a relatively high proportion (54%) of patients with complicated appendicitis and the relatively low recovery of anaerobic pathogens. Also, the majority of patients had APACHE II scores of <10. Further clinical evaluation of eravacycline treatment in more severely ill patients and patients with more complex infections employing improved anaerobic culture methodology are planned.

In conclusion, data from this phase 2 study support the continued development of eravacycline for the treatment of serious infections, including those caused by drug-resistant Gram-negative pathogens. The results of this study, together with the pharmacokinetic analyses, will help to adequately inform the design of the pivotal phase 3 study of eravacycline for the treatment of cIAIs.

ACKNOWLEDGMENTS

This study was sponsored by Tetraphase Pharmaceuticals.

Joseph S. Solomkin has received consulting fees from Tetraphase Pharmaceuticals. Joyce A. Sutcliffe, Susannah M. Walpole, and Patrick T. Horn are employees of Tetraphase Pharmaceuticals.

Medical writing support was provided by Kimberley Severin of the International Surgical Infections Study Group.

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