Presentation 264
Monday

Intravenous Eravacycline with Transition to Oral Therapy for Treatment of Complicated Urinary Tract Infections (cUTI) Including Pyelonephritis: Results from a Randomized, Double-Blind, Multicenter, Phase 3 Trial (IGNITE2)

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Abstract

Background: Eravacycline (ERV) is a novel, fully synthetic fluorocycline antibiotic of the tetracycline class with broad-spectrum activity being developed for the treatment of serious infections, including those caused by multidrug-resistant pathogens.

Methods: IGNITE2 evaluated the efficacy and safety of ERV vs levofloxacin (LEV) in hospitalized patients with cUTI. Patients were randomized to intravenous (IV) ERV 1.5 mg/kg once daily (QD) or IV LEV 750 mg QD. Patients could transition to ERV 200 mg orally (PO) twice daily or LEV 750 mg PO QD after 3 days if clinically indicated, for a total of 7 days. The primary endpoint was the composite response rate (clinical cure and microbiological success) in the microbiological intent-to-treat (micro-ITT) population at the post-treatment visit (PT, 6-8 days after end of therapy [EOT]) with a non-inferiority margin of 10%.

Results: 908 patients were randomized, 600 were included in micro-ITT analysis. Although composite response rates were higher for ERV than LEV at EOT (Δ=5.5%, 95% CI=-0.5 to 11.4), ERV did not achieve non-inferiority to LEV at PT. In a pre-specified subgroup analysis, the response rate among LEV-resistant pathogens was higher for ERV compared to LEV. Response rates were also higher for ERV among patients who received 7 days of IV study drug.

Table 1. Composite Response at the PT Visit

Group	ERV	LEV	Δ (95% CI)
All micro-ITT	180/298 (60.4%)	202/302 (66.9%)	-6.5% (-14.1, 1.2)
LEV-R pathogens	43/80 (53.8%)	31/85 (36.5%)	17.3 (2.1, 31.8)
3 days IV	74/131 (56.5%)	91/129 (70.5%)	-14.1% (-25.4, -2.3)
7 days IV	30/51 (58.8%)	26/54 (48.2%)	10.7% (-8.5, 29.0)

The most common adverse events were nausea and vomiting, 82/455 (18%) and 33/455 (7.3%) for ERV vs 14/450 (3.1%) and 6/450 (1.3%) for LEV, respectively.

Conclusions: ERV did not achieve statistical non-inferiority compared to LEV but showed higher response rates among patients with LEV-resistant pathogens and those who received 7 days of IV study drug. Further investigation of the change in response between EOT and PT and the efficacy of IV-only therapy is warranted.

Introduction

Urinary tract infections (UTIs) are among the most common infectious diseases, affecting approximately 150 million people each year worldwide and necessitating approximately 10.5 million physician visits per year in the US.[1] Catheter-associated UTI (CA-UTI) is the most frequent healthcare–associated infection worldwide, accounting for up to 40% of hospital-acquired infections in US hospitals each year.[2] A large proportion of prescribed antibiotics in the United States and Europe are dispensed for UTIs, and the prevalence of antimicrobial resistance among urinary tract pathogens limits treatment options.[3,4]

Eravacycline (ERV) is a novel, fully-synthetic fluorocycline antibiotic of the tetracycline class being developed for the treatment of serious infections, including those caused by extended-spectrum beta-lactamase (ESBL) and carbapenemase-producing Enterobacteriaceae as well as multidrug-resistant (MDR) strains of *Acinetobacter baumannii*.[5]

The present study was designed to assess the efficacy and safety of eravacycline compared with levofloxacin in subjects diagnosed with cUTI.

A lead-in portion of this study was completed in which subjects were randomized (1:1:1) to receive eravacycline (ERV) 1.5 mg/kg intravenously (IV) every 24 hours followed by 200 mg ERV orally every 12 hours, ERV 1.5 mg/kg IV every 24 hours followed by 250 mg ERV orally every 12 hours, or levofloxacin (LEV) 750 mg IV every 24 hours followed by LEV 750 mg orally every 24 hours.[6]

Based on pharmacokinetic and tolerability profiles, the dosage carried forward to the pivotal portion of the study was ERV 200 mg orally every 12 hours. Subsequently, subjects were randomized (1:1) to receive ERV 1.5 mg/kg intravenously (IV) every 24 hours followed by 200 mg ERV orally every 12 hours, or LEV 750 mg IV every 24 hours followed by LEV 750 mg orally every 24 hours.

Methods

- Randomization system/blinding
  - Randomized, double-blind, double-dummy, multicenter, prospective study
  - Stratified based on the primary site of infection and receipt of a single dose of effective non-study antibiotics within 24 hours of enrollment
- Key Inclusion Criteria
  - Male and female subjects >18 years of age who were able to provide informed consent
  - Had either pyelonephritis and normal urinary tract anatomy or cUTI with at least one of the following conditions:
    - Indwelling urinary catheter
    - Urinary retention (at least approximately 100 mL of residual urine after voiding)
    - History of neurogenic bladder
    - Partial obstructive uropathy (e.g., nephrolithiasis, bladder stones, and ureteral strictures)
    - Azotemia of renal origin (not congestive heart failure or volume related) such that the serum blood urea nitrogen (BUN) was elevated (> 20 mg/dL) AND the serum BUN:creatinine ratio was < 15
    - Surgically modified or abnormal urinary tract anatomy (e.g., bladder diverticula, redundant urine collection system, etc.) EXCEPT urinary tract surgery within the month prior to screening (placing of stents or catheters was not considered to be surgical modification)
  - Had at least two of the following signs or symptoms:
    - Chills, rigors, or warmth associated with fever (oral, rectal, tympanic, or temporal artery temperature > 100.4°F/38°C) or hypothermia (oral, rectal, tympanic, or temporal artery temperature < 95°F/35°C)
    - Flank pain (pyelonephritis) or pelvic pain (cUTI)
    - Nausea or vomiting
    - Dysuria, urinary frequency, or urinary urgency
    - Costovertebral angle tenderness on physical examination
  - Had a urine specimen with evidence of pyuria as indicated by any of the following:
    - Dipstick analysis positive for leukocyte esterase (where positive result was at least "++" as indicated on the urine dipstick provided in the laboratory kit), OR
    - At least 10 white blood cells (WBCs) per cubic millimeter, OR
    - ≥ 10 WBCs per high power field
- Key Exclusion Criteria
  - Concurrent use of non-study antibacterial drug therapy that would have had a potential effect on outcome evaluations in subjects with cUTI, including:
    - Subjects who had a history of levofloxacin-resistant urinary tract infection
    - Were likely to receive ongoing antibacterial drug prophylaxis prior to the LPT visit (e.g., subjects with vesiculo-ureteral reflux)
    - Had use of systemic antibiotics effective in cUTI within 72 hours prior to enrollment except under specific circumstances
  - Complicated pyelonephritis with complete obstruction or known or suspected renal or perinephric abscess, emphysematous pyelonephritis, OR
    - Any condition that was likely to have required surgery to achieve cure (this did NOT include procedures to place catheters or obtain diagnosis)
  - Subjects who had a high risk for cUTI due to *Pseudomonas* spp.
  - Neutropenia (absolute neutrophil count < 1,000 PMNs/μL)
  - Creatinine clearance of < 50 mL/min as estimated by the Cockcroft-Gault equation (eCCr)
  - Had a known or suspected hypersensitivity to tetracyclines or fluoroquinolones
- Primary and Secondary Endpoints
  - Primary Objective, FDA: To demonstrate that eravacycline is non-inferior to levofloxacin in responder outcome (clinical and microbiological response vs failure) in the microbiological intent-to-treat (micro-ITT) population at the Post-Treatment (PT) visit (defined as 6-8 days after the completion of therapy)
  - Primary Objective, EMA: To demonstrate that eravacycline is non-inferior to levofloxacin in microbiological response in the microbiological modified ITT (micro-MITT) and microbiologically evaluable (ME) populations at the PT visit
  - Secondary Objectives:
    - To compare clinical response for subjects in the treatment groups at the Dose Cycle 3, End of Intravenous (IV) Therapy (EOI), End of Therapy (EOT), PT, and Late Post-Treatment (LPT) visits
    - To compare time to resolution of signs and symptoms by treatment group
    - To compare microbiological response in the treatment groups at the Dose Cycle 3, EOI, EOT, PT, and LPT visits
    - To assess the safety and tolerability of eravacycline administration in the safety population
    - To test for superiority of eravacycline over levofloxacin in the treatment of complicated urinary tract infection (cUTI):
      - For the subset of subjects with infections caused by quinolone-resistant pathogens, eravacycline will be compared with levofloxacin in responder outcome in the micro-ITT, micro-MITT, and ME populations at the PT visit
    - To explore pharmacokinetic (PK) parameters of eravacycline

Figure 1. IGNITE2 Study Design

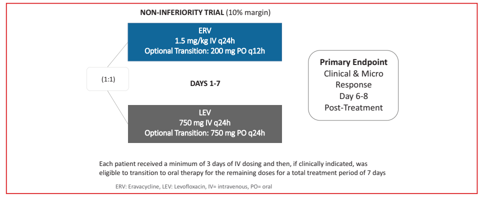


Table 1. Analysis Population Definitions

Intent to Treat (ITT)	All subjects randomized
Microbiological Intent to Treat (micro-ITT*)	All subjects in the ITT population who had at least one baseline bacterial pathogen on culture of urine or blood that causes urinary tract infection against which the investigational drug has expected antibacterial activity
Microbiological Modified Intent to Treat (micro-MITT ꞌ)	All subjects in the micro-ITT population who received at least one dose of study drug
Clinically Evaluable (CE)	All subjects in the ITT population who met key inclusion/exclusion criteria, received correct study drug, had clinical outcome assessed, and followed other important components of the trial
Microbiologically Evaluable (ME)ꞌ	All subjects in the micro-ITT population who met key inclusion/exclusion criteria, received correct study drug, had microbiological outcome assessed, and followed other important components of the trial
Safety	All subjects who received any amount of study drug

*FDA Primary Analysis Population
ꞌEMA Primary Analysis populations

Results

Figure 2. Patient Flow and Study Populations

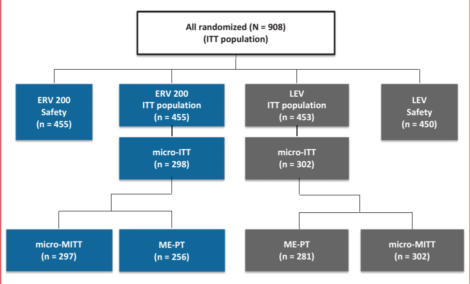


Table 2. Baseline Patient Demographics (ITT)

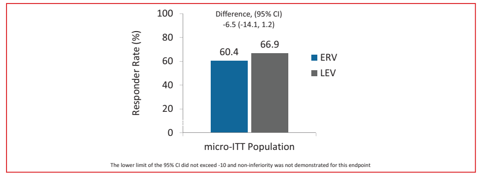
	Eravacycline (N=455)	Levofloxacin (N=453)
Age (years), mean (min, max)	53.7 (18, 89)	51.7 (18, 88)
Race (% Caucasian)	95.4	95.6
Gender (% male)	36	33.3
Height (cm), mean*	167.43	167.98
Weight (kg), mean*	76.18	75.30
BMI (kg/m^2), mean*	27.13	26.66

*n=454 for Eravacycline, 451 for Levofloxacin

Table 3. cUTI Diagnosis/Conditions at Enrollment (ITT)

	Eravacycline (N=455) n (%)	Levofloxacin (N=453) n (%)
Acute pyelonephritis	221 (48.8)	226 (50)
Other cUTI	234 (51.2)	227 (50)
Obstructive uropathy	109 (24)	94 (20.1)
Surgical/abnormal anatomy	76 (16.7)	68 (15)
Urinary retention	73 (16)	75 (16.6)
Neurogenic bladder	28 (6.2)	31 (6.8)
Indwelling urinary catheter	18 (4)	14 (3.1)
Azotemia	3 (0.7)	-
Other	-	1 (0.2)

Figure 3. FDA Primary Efficacy Endpoint: Response at Post-Treatment Visit (micro-ITT)



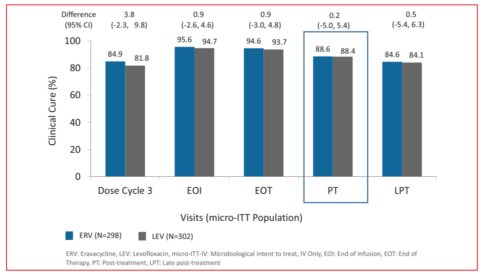
The lower limit of the 95% CI did not exceed -10 and non-inferiority was not demonstrated for this endpoint

Table 4. Responder Rate at All Visits (micro-ITT)

Visit	Response	ERV (N=298) n (%)	LEV (N=302) n (%)	Difference (95% CI)
Dose Cycle 3	Responder	241 (80.9)	215 (71.2)	9.7 (2.9, 16.5)
	Non-responder	48 (16.1)	80 (26.5)	
	Indeterminate/Missing	9 (3)	7 (2.3)	
EOI	Responder	271 (90.9)	254 (84.1)	6.8 (1.6, 12.2)
	Non-responder	23 (7.7)	43 (14.2)	
	Indeterminate/Missing	4 (1.3)	5 (1.7)	
EOT	Responder	258 (86.6)	245 (81.1)	5.5 (-0.5, 11.4)
	Non-responder	29 (9.7)	50 (16.6)	
	Indeterminate/Missing	11 (3.7)	7 (2.3)	
PT*	Responder	180 (60.4)	202 (66.9)	-6.5 (-14.1, 1.2)
	Non-responder	100 (33.6)	91 (30.1)	
	Indeterminate/Missing	18 (6.0)	9 (3.0)	
LPT	Responder	146 (49)	179 (59.3)	-10.3 (-18.21, -2.35)
	Non-responder	135 (45.3)	114 (37.8)	
	Indeterminate/Missing	17 (5.7)	9 (3)	

*FDA Primary Analysis Population
EOI= End of Infusion, EOT= End of Therapy, PT= Post-treatment, LPT= Late Post-Treatment

Figures 4 and 5. Secondary Efficacy Endpoints: Clinical and Microbiological Outcomes at All Visits (micro-ITT)



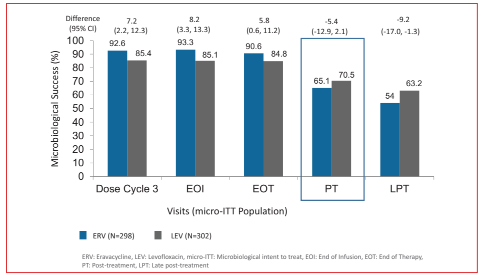


Table 5. EMA Co-Primary Efficacy Endpoints: Microbiological Success at Post-Treatment Visit (micro-MITT and ME)

Population	Response	ERV (N=297) n (%)	LEV (N=302) n (%)	Difference (99% CI)
micro-MITT	Microbiological Success	194 (65.3)	213 (70.5)	-5.2 (-14.6, 4.8)
	Failure	85 (28.6)	78 (25.8)	
	Indeterminate/Missing	18 (6.1)	11 (3.6)	
ME*	Microbiological Success	180 (70.6)	203 (73.6)	-3.0 (-12.0, 7.7)
	Failure	76 (29.7)	78 (27.8)	

*n=255 for Eravacycline, 276 for Levofloxacin

Table 6. Baseline Pathogens from Blood and Urine Cultures, >2.5% in ERV Group (micro-ITT)

Pathogen Type / Pathogen	ERV (N = 298) n (%)	LEV (N = 302) n (%)
Gram-negative aerobes	276 (92.6)	271 (89.7)
Enterobacteriaceae	273 (91.6)	267 (88.4)
Escherichia coli	222 (74.5)	217 (71.9)
Klebsiella pneumoniae	29 (9.7)	27 (8.9)
Proteus mirabilis	8 (2.7)	13 (4.3)
Gram-positive aerobes	32 (10.7)	36 (11.9)
Enterococcus faecalis	18 (6.0)	19 (6.3)
Staphylococcus epidermidis	8 (2.7)	3 (1.0)
Quinolone-resistant pathogens	80 (26.8)	85 (28.1)

micro-ITT = microbiological intent-to-treat; N = number of subjects in the micro-ITT analysis population; n = number of subjects in the subgroup or treatment group;
Notes: Percentages are calculated as 100 × <n/N).Subjects with the same pathogen from more than one specimen are counted only once for that pathogen. Subjects with polymicrobial cultures are represented multiple times within the table (with each pathogen). Subjects are counted only once in the overall tabulation of Gram-negative aerobes, Gram-positive aerobes, and quinolone-resistant pathogens. Subjects are counted only once for the overall tabulation of *Enterobacteriaceae*.

Figure 6. Per Pathogen Outcome at Post-Treatment Visit (micro-ITT)

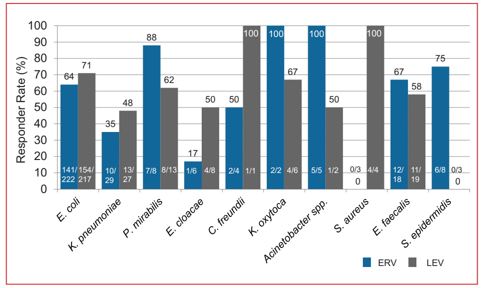


Table 7. Response at Post-Treatment for Quinolone-resistant Pathogens (micro-ITT)

Response	ERV (N=80) n (%)	LEV (N=85) n (%)	Difference (95% CI)
Responder	43/80 (53.8)	31/85 (36.5)	17.3 (2.1, 31.8)
Non-responder	35/80 (43.8)	54/85 (63.5)	
Indeterminate/Missing	2/80 (2.5)	0/85 (0.0)	

Figure 7. Responder Rates by Duration of IV Study Drug (micro-ITT)

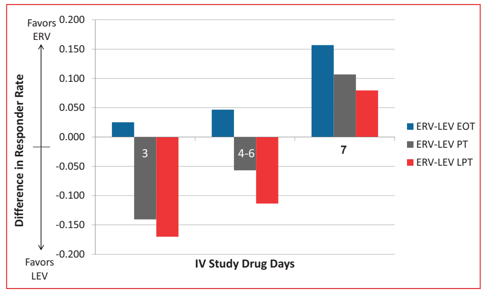


Table 8. Overall Safety and Incidence of TEAEs Occurring in ≥1% in Either Arm (Safety)

Type of AE	ERV (N=455) n (%)	LEV (N=450) n (%)
Number of subjects who experienced at least 1 AE	169 (37.1)	102 (22.7)
TEAE	169 (37.1)	99 (22)
Gastrointestinal Disorders (SOC)	110 (24.2)	36 (8)
Nausea	82 (18)	14 (3.1)
Vomiting	33 (7.3)	6 (1.3)
General disorders/Administrative site conditions (SOC)	24 (5.3)	15 (3.3)
Headache	14 (3.1)	6 (1.3)
Hypertension	8 (1.8)	4 (0.9)
TEAE related to study drug	121 (26.6)	50 (11.1)
TEAE leading to premature discontinuation of study drug	15 (3.3)	10 (2.2)
Serious TEAE (SAE)	7 (1.5)	6 (1.3)
SAE leading to premature discontinuation of study drug	2 (0.4)	3 (0.7)
SAE leading to death	1 (0.2)	-

AE= Adverse Event, TEAE= Treatment-emergent Adverse Event

Conclusions

- Eravacycline was well-tolerated. The most frequently reported adverse events with eravacycline were gastrointestinal disorders, primarily nausea and vomiting. These events rarely led to study drug discontinuation.
- Eravacycline did not achieve the primary efficacy endpoint of statistical non-inferiority compared with levofloxacin in responder rate at the PT visit in the micro-ITT population.
- Responder rates through the end of therapy favored eravacycline; responder rates at subsequent timepoints favored levofloxacin.
- Responder rates at the PT visit for subjects with quinolone-resistant pathogens were higher in the eravacycline arm (53.8%) than in the levofloxacin arm (36.5%). The between-treatment group difference favored eravacycline and the lower limit of the 95% CI exceeded zero, consistent with superiority of eravacycline to levofloxacin in this subgroup.
- Responder rates by duration of IV study drug suggested more favorable outcomes with more days of IV eravacycline. Further investigation is warranted.

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