Presentation 265
Monday

Intravenous Eravacycline Compared to Intravenous Levofloxacin for the Treatment of Complicated Urinary Tract Infections (cUTI): Subgroup Analysis from a Randomized, Double-Blind, Phase 3 Trial (IGNITE2)

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Abstract

Background: In IGNITE2, eravacycline (ERV), when administered as an intravenous (IV) to oral transition therapy, did not achieve the primary endpoint of statistical non-inferiority compared to levofloxacin (LEV) for the treatment of cUTI. Additionally, fewer days of IV therapy was associated with loss of efficacy between the end of therapy (EOT) and post treatment (PT, 6-8 days after EOT) evaluations, particularly among ERV patients.

METHODS: A subgroup analysis of patients enrolled in IGNITE2 who received only IV ERV 1.5 mg/kg once daily or IV LEV 750 mg once daily was performed. All patients who received IV-only therapy were included, regardless of the duration of treatment.

RESULTS: There were 178 patients who received IV-only therapy; 121 were included in the microbiological intent-to-treat (micro-ITT) population. Baseline demographics were balanced between the 2 groups and included 67% female, mean age 58.3±16.9 years, and 38% pyelonephritis. *Escherichia coli* was the most common pathogen identified (76.5%). The LEV resistance rate was 34.7%. Composite responder rates (clinical cure and microbiological success) at PT are presented in Table 1. Responder rates among patients with LEV-resistant and LEV-susceptible pathogens are also presented. The most common adverse events were nausea and vomiting, reported in 19/91 (20.9%) and 8/91 (8.8%) subjects in the ERV arm compared to 6/87 (6.9%) and 3/87 (3.4%) subjects in the LEV arm.

Table 1. Composite Response at the PT Visit – IV-Only Therapy

Group	ERV	LEV	Δ (95% CI)
IV-only micro-ITT	31/57 (54.4%)	27/64 (42.2%)	12.2% (-5.7, 29.3)
LEV-R pathogens	8/19 (42.1%)	3/23 (13.0%)	29.1% (2.1, 53.8)
LEV-S pathogens	23/38 (60.5%)	24/41 (58.5%)	2.0% (-19.5, 23.2)

CONCLUSIONS: ERV demonstrated comparable efficacy to LEV in a subgroup of patients enrolled in IGNITE2 who received IV-only therapy for the treatment of cUTI and greater efficacy in patients with LEV-resistant pathogens.

Introduction

IGNITE2 was a phase 3 study designed to assess the safety and efficacy of eravacycline (ERV) administered as an intravenous (IV) to oral (PO) transition therapy compared with levofloxacin (LEV) in subjects diagnosed with cUTI (Refer to P264). In the pivotal portion of the study, responder rates were 60.4% for the ERV arm and 66.9% for the LEV arm in the microbiological intent-to-treat (micro-ITT) population at the Post-Treatment (PT) visit. The resulting difference was −6.5% (95% CI: −14.1, 1.2). The lower limit of the 95% CI did not exceed −10%, and non-inferiority was not demonstrated.

Responder rates at earlier timepoints (through the end of therapy) favored ERV. At the PT visit, there was a disproportionate loss of efficacy in the ERV arm, such that responder rates now favored LEV.

Tetraphase conducted several post hoc analyses in order to better understand the reasons for the disproportionate loss of efficacy, including the development of a logistic regression model to identify factors associated with loss of efficacy between EOT and PT. The results of these analyses indicated that treatment with more days of IV ERV was associated with improved efficacy relative to levofloxacin (Refer to P266).

To further explore this hypothesis, a post hoc subset of subjects from IGNITE2 who were administered IV study drug, but who never transitioned to PO study drug, was identified to analyze the efficacy and safety of IV-only ERV in the treatment of cUTI.

Methods

- Post hoc assessment of subjects enrolled in IGNITE2 who received IV study drug only
- All subjects who received IV study drug and did not receive PO study drug were included, regardless of duration of therapy or reason for study drug discontinuation
- Key Inclusion Criteria for IV-Only Population
  - All subjects who received 7 days of IV study drug or discontinued study drug for any reason prior to beginning PO study drug
  - 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 for IV-Only Population
  - Receipt of any PO study drug
  - 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:
    - The number and percentage of subjects in each treatment group defined as responder (clinical cure and microbiologic success), non-responder, and indeterminate/missing were tabulated
    - Methods identical to those for the overall micro-ITT population
    - Additional assessments conducted by stratification of primary site of infection and use of single effective dose of prior antibiotic (including additional sensitivity analyses)
  - Primary Objective, EMA:
    - Methods identical to those for overall micro-MITT and ME populations
    - Additional assessments conducted by stratification of primary site of infection and use of single effective dose of prior antibiotic (including additional sensitivity analyses)
  - 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 assess primary and secondary efficacy outcomes at PT visit by treatment group, baseline pathogen(s), and quinolone-resistant pathogens

Results

Figure 1. IGNITE2 IV-Only Post-hoc Study Design

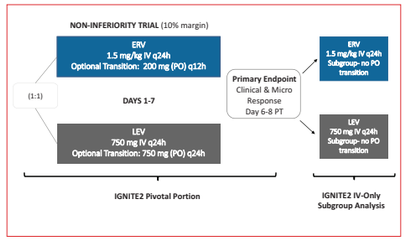


Table 1. Analysis Population Definitions

ITT-IV	Intent to Treat, IV-Only	All subjects randomized who received only IV study drug
micro-ITT-IV*	Microbiological Intent to Treat, IV-Only	All subjects in the ITT-IV 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
micro-MITT-IV†	Microbiological Modified Intent to Treat, IV-Only	All subjects in the micro-ITT-IV population who received at least one dose of study drug
CE-IV	Clinically Evaluable, IV-Only	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
ME-IV†	Microbiologically Evaluable, IV-Only	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-IV	Safety Population, IV-Only	All subjects randomized who received any amount of IV only study drug

*FDA Primary Analysis Population
†EMA Primary Analysis population

Figure 2. IGNITE2 IV-Only Subjects

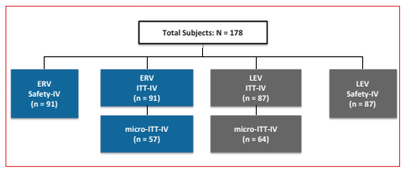
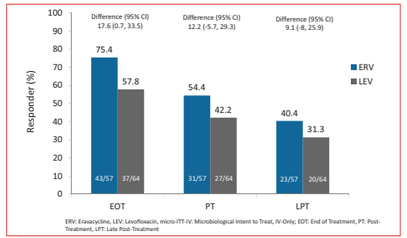


Table 2. Baseline Patient Demographics (ITT-IV)

	Eravacycline (N=91)	Levofloxacin (N=87)
Age (years), mean (min, max)	58.7	55.2
Race (% Caucasian)	84 (92.3)	82 (94.3)
Gender (% male)	33 (36.3)	31 (35.6)
Height (cm), mean	166.3	168.2
Weight (kg), mean	76.9	79.7
BMI (kg/m²), mean	27.8	28.2
Acute Pyelonephritis (%)*	24 (42.1)	22 (34.4)
Other cUTI (%)*	33 (57.9)	42 (65.6)

*For micro-ITT-IV population, n=57 for eravacycline, n=64 for levofloxacin

Figure 3. IV-Only Responder Outcome at End of Therapy, Post-Treatment, and Late Post-Treatment (micro-ITT-IV)



ERV: Eravacycline, LEV: Levofloxacin, micro-ITT-IV: Microbiological Intent to Treat, IV-Only; EOT: End of Treatment, PT: Post-Treatment, LPT: Late Post-Treatment

Table 3. IV-Only Responder Rate at All Visits (micro-ITT-IV)

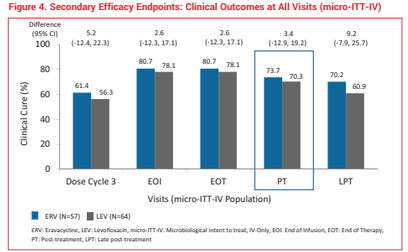
Visit	Response	ERV (N=57) n (%)	LEV (N=64) n (%)	Difference (95% CI)
Dose Cycle 3	Responder	33 (57.9)	27 (42.2)	15.7 (-2.2, 32.6)
	Non-responder	20 (35.1)	34 (53.1)	
	Indeterminate/Missing	4 (7.0)	3 (4.7)	
EOT	Responder	43 (75.4)	37 (57.8)	17.6 (0.7, 33.5)
	Non-responder	13 (22.8)	24 (37.5)	
	Indeterminate/Missing	1 (1.8)	3 (4.7)	
PT*	Responder	31 (54.4)	27 (42.2)	12.2 (-5.7, 29.3)
	Non-responder	24 (42.1)	34 (53.1)	
	Indeterminate/Missing	2 (3.5)	3 (4.7)	
LPT	Responder	23 (40.4)	20 (31.3)	9.1 (-8.0, 25.9)
	Non-responder	32 (56.1)	41 (64.1)	
	Indeterminate/Missing	2 (3.5)	3 (4.7)	

*FDA Primary Analysis Population

Table 4. IV-Only Responder Rate at PT by Primary Site of Infection (micro-ITT-IV)

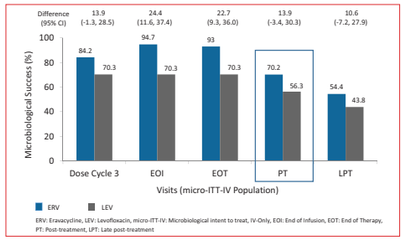
Primary Site of Infection	Response	ERV (N=57) n (%)	LEV (N=64) n (%)	Difference (95% CI)
Pyelonephritis and normal urinary tract anatomy	n	24	22	
	Responder	14 (58.3)	12 (54.5)	3.8 (-24.3, 31.4)
	Non-responder	9 (37.5)	8 (36.4)	
	Indeterminate/Missing	1 (4.2)	2 (9.1)	
All other cUTI diagnoses	N	33	42	
	Responder	17 (51.5)	15 (35.7)	15.8 (-6.8, 37.1)
	Non-responder	15 (45.5)	26 (61.9)	
	Indeterminate/Missing	1 (3.0)	1 (2.4)	

Figure 4. Secondary Efficacy Endpoints: Clinical Outcomes at All Visits (micro-ITT-IV)



ERV: Eravacycline, LEV: Levofloxacin, micro-ITT-IV: Microbiological intent to treat, IV-Only, EOI: End of Infusion, EOT: End of Therapy, PT: Post-treatment, LPT: Late post-treatment

Figure 5. Secondary Efficacy Endpoints: Microbiological Outcomes at All Visits (micro-ITT-IV)



ERV: Eravacycline, LEV: Levofloxacin, micro-ITT-IV: Microbiological intent to treat, IV-Only, EOI: End of Infusion, EOT: End of Therapy, PT: Post-treatment, LPT: Late post-treatment

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

Population	Response	ERV (N=57) n (%)	LEV (N=64) n (%)	Difference (99% CI)
micro-MITT	Microbiological Success	40 (70.2)	36 (56.3)	13.9 (-9.8, 34.2)
	Failure	14 (24.6)	25 (39.1)	
	Indeterminate/Missing	3 (5.3)	3 (4.7)	
ME*	Microbiological Success	36 (75.0)	31 (56.4)	18.6 (-7.4, 39.4)
	Failure	12 (25.0)	24 (43.6)	

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

Pathogen Type Pathogen	ERV (N = 57) n (%)	LEV (N = 64) n (%)
Gram-negative aerobes	52 (91.2)	59 (92.2)
Enterobacteriaceae	52 (91.2)	57 (89.1)
Escherichia coli	41 (71.9)	44 (68.8)
Klebsiella pneumoniae	6 (10.5)	9 (14.1)
Citrobacter freundii	2 (3.5)	0 (0.0)
Proteus mirabilis	2 (2.5)	3 (4.7)
Gram-positive aerobes	5 (8.8)	7 (10.9)
Enterococcus faecalis	3 (5.3)	5 (7.8)
Enterococcus species	2 (3.5)	0 (0.0)
Quinolone-resistant pathogens	19 (33.3)	23 (35.9)

micro-ITT-IV = microbiological intent-to-treat, IV Only; N = number of subjects in the micro-ITT-IV 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*.

Table 7. Response at PT for Quinolone-resistant Pathogens (micro-ITT-IV)

Populations	Response	ERV (N=19) n (%)	LEV (N=23) n (%)	Difference (95% CI)
Quinolone-resistant	Responder	8 (42.1)	3 (13.0)	29.1 (2.1, 53.8)
	Non-responder	11 (57.9)	20 (87.0)	
	Indeterminate/Missing	0 (0.0)	0 (0.0)	
Non-quinolone-resistant	Responder	23 (60.5)	24 (58.5)	2.0 (-19.5, 23.2)
	Non-responder	13 (34.2)	14 (34.2)	
	Indeterminate/Missing	2 (5.3)	3 (7.3)	

Table 8. Overall Safety and Incidence of TEAEs Occurring in ≥2% in Either Arm (Safety-IV)

Type of AE	ERV (N=91) n (%)	LEV (N=87) n (%)
Number of subjects who experienced at least 1 AE	41 (45.1)	28 (32.2)
TEAE	41 (45.1)	28 (32.2)
Gastrointestinal Disorders (SOC)	27 (29.7)	15 (17.2)
Nausea	19 (20.9)	6 (6.9)
Vomiting	8 (8.8)	3 (3.4)
Dyspepsia	4 (4.4)	0 (0.0)
Upper abdominal pain	2 (2.2)	2 (2.3)
Diarrhea	2 (2.2)	7 (8.0)
General disorders/Administrative site conditions (SOC)	8 (8.8)	4 (4.6)
Headache	4 (4.4)	0 (0.0)
Infusion site phlebitis	3 (3.3)	0 (0.0)
Peripheral edema	0 (0.0)	2 (2.3)
TEAE related to study drug	32 (35.2)	16 (18.4)
TEAE leading to premature discontinuation of study drug	4 (4.4)	4 (4.6)
Serious TEAE (SAE)	1 (1.1)	3 (3.4)
SAE leading to premature discontinuation of study drug	0 (0.0)	2 (2.3)
SAE leading to death	0 (0.0)	0 (0.0)

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

Conclusions

- The pre-specified primary and secondary efficacy analyses for IGNITE2 were repeated for the IV-only population.
  - In the post-hoc analysis of the responder rate at the PT visit in the micro-ITT-IV population, the between treatment group difference was 12.2% (95% CI: -5.7, 29.3), favoring eravacycline. The lower limit of the 95% CI exceeded the -10% NI margin specified in the planned analysis.
  - In the post-hoc analysis of the microbiological success rates at the PT visit in the micro-MITT-IV and ME-PT-IV populations, the between treatment group differences were 13.9% (adjusted 99% CI: -9.8, 34.2) and 18.6% (adjusted 99% CI: -7.4, 39.4), favoring eravacycline. The lower limits of the 99% CIs exceeded the -10% NI margin specified in the planned analysis.
- The safety profile in the IV-only population was generally similar to that in the Safety population for the overall study.
- The results of the analyses among subjects who received only IV study drug support further study of IV-only eravacycline for the treatment of cUTI.

References

1. Tsai L, Zervos M, Miller L, et al. Abstract 264. ASM Microbe 2016, Boston, MA, June 16-20, 2016.
2. Tsai L, Das A, Mohr J, et al. Abstract 266. ASM Microbe 2016, Boston, MA June 16-20, 2016.