Poster # 1832

Impact of Meal Timing on Eravacycline Exposure During the Oral Portion of an IV to Oral Transition Dosing Regimen

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Abstract

Background: Eravacycline (ERV) is a novel fluorocycline being developed for the treatment of serious infections, including those caused by MDR pathogens. Multivariate analysis of data from a phase 3 study of ERV in complicated urinary tract infection (IGNITE2) indicated that the oral dosing component drove the overall study results in which the primary efficacy endpoint was not achieved. We investigated ERV exposure following oral dosing under conditions of the phase 3 study.

Methods: This was a two-period cross-over study in healthy subjects. In both periods subjects received ERV: 3 doses of 1.5 mg/kg IV q24h followed by 9 doses of 200 mg oral q12h with the first oral dose 12h after the last IV dose. In one period (fasted) subjects were fasted at least 4h prior to oral doses and in the other period (fed) the subjects were fed as in the previous phase 3 study; 2h prior to dosing. Plasma and 24h urine were collected on Days 1, 3 and 7.

Results: The following exposures [mean(%CV)] were observed:

Day	Fed				Fasted			
	Cmax (ng/mL)	AUC (ng*h/mL)			Cmax (ng/mL)	AUC (ng*h/mL)		
		0-12	12-24	0-24		0-12	12-24	0-24
1	2360 (23)	5530 (17)		7020 (17)	2280 (29)	5440 (23)		6980 (22)
3	2760 (27)	7020 (21)	2540 (19)	9610 (19)	2520 (29)	6760 (22)	2890 (17)	9700 (19)
7	152 (36)	1330 (38)	1430 (32)	2780 (33)	254 (38)	2240 (33)	2210 (31)	4490 (29)

	Day 1		Day 3		Day 7	
	0-12 h	12-24 h	0-12 h	12-24 h	0-12 h	12-24 h
Fed	12.2	5.3	20.6	9.5	8	7.5
Fasted	11.8	5.2	21.4	12.7	14	12

In the fasted period, Day 7 AUC_{0-24} was 65% of Day 1, and both exposure and urine concentrations are in the expected therapeutic range. In the fed period, Day 7 AUC_{0-24} is 39% of Day 1 and both exposure and urine concentrations are likely below the therapeutic range.

The safety profile of ERV was similar to that observed in previous phase 1 studies.

Conclusions: These results support the conclusion that oral dosing in the previous phase 3 study resulted in low ERV exposures and urine concentrations. The exposures and urine concentrations observed with IV ERV are well within the expected therapeutic range and support the efficacy of IV ERV in the treatment of cUTI. Day 7 results in the fasted period indicate that an IV to oral transition dose regimen for ERV is achievable and work is ongoing to optimize dose and meal schedule.

Introduction

Eravacycline (ERV) is a novel, fully-synthetic fluorocycline antibiotic being developed for the treatment of serious and life-threatening infections, including those caused by multidrug-resistant pathogens. In a recent Phase 3 study (IGNITE2) examining the efficacy and safety of ERV administered as IV-to-oral treatment for cUTI, ERV did not meet the primary efficacy endpoint. Post-hoc analyses support the conclusion that overall study results were driven by the underperformance of the oral formulation of ERV under the experimental conditions of the study.[1-3] The purpose of this study was to further investigate IV-to-oral formulations of ERV under fed and fasted conditions to better understand the results from the IGNITE2 study and guide further development of ERV oral formulations.

Methods

- Phase 1, single site, randomized, open-label, inpatient, crossover study in healthy subjects

Primary Objective: assess the PK profile of IV-to-oral ERV in healthy adult volunteers in the fed versus fasted state

Secondary Objective: assess safety and tolerability of IV and oral ERV in fed and fasted healthy adult volunteers

Key Inclusion Criteria

- Adults, age 18-55 years
- Non-obese; Body Mass Index (BMI) of 18 to 30 kg/m^2
- Non-childbearing potential
- Negative for HIV or Hepatitis (B, C)
- Signed consent form

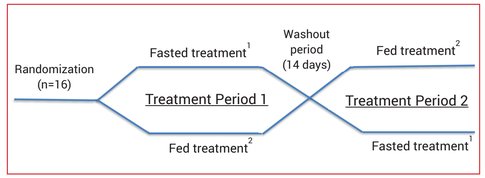
Key Exclusion Criteria

- History or presence of clinically significant disease or disorder
- Lab, blood pressure, heart rate or ECG values abnormal or outside of reference ranges
- Use of another investigational drug or device
- Consumption of nicotine, alcohol or drug abuse substances

- Subjects were randomized in a 1:1 ratio into either the fasted/fed or fed/fasted ERV treatment group receiving ERV 1.5 mg/kg IV daily Days 1-3 and 200 mg oral twice daily Days 3-7 with the first oral dose 12 hours after the last IV dose (Figure 1).
- Plasma and urine samples for pharmacokinetic (PK) analyses were collected on Days 1, 3 and 7 of both fed and fasted treatment periods.
- Safety was assessed through collection of adverse events (AEs), clinical labs, vital signs, ECG and physical exam data.

Methods (cont'd)

Figure 1. Study Design



[1] Fasted conditions: AM dose given after overnight fast with 4-hr post-dose fast. PM dose given after 4-hr pre-dose fast with 2-hr post-dose fast.

[2] Fed conditions: AM dose given 2 hours after breakfast with 1-hour post-dose fast. PM dose given after 2-hour pre-dose fast with 1-hour post-dose fast.

Results

Study Population

- A total of 16 subjects were enrolled in the study, with 7 subjects in each arm completing the study.
- Demographics and baseline characteristics were generally similar across treatment groups
  - Majority of subjects were male (15 subjects, 93.8%); Mean age was 38.1 years (range: 22 to 55 years); Predominant race was African American (9 subjects, 56.3%); Mean BMI was 25.87 kg/m^2

Pharmacokinetic Results

- In the fasted period, Day 7 AUC_{0-24} was 65% of Day 1, and both exposure and urine concentrations were in the expected therapeutic range. In the fed period, Day 7 AUC_{0-24} was 39% of Day 1 and both exposure and urine concentrations were likely below the therapeutic range.
- For the oral dosing portion of ERV, the observed plasma concentrations and urine concentrations were lower in the fed treatment compared to the fasted treatment period.
- Changes in mean C_{max} of ERV following oral administration on Day 3 (PM), Day 7 (AM) and Day 7 (PM) in fed vs. fasted subjects were 22.8%, 39.6%, and 44.8%, respectively.

Results

Table 2. Mean (CV%) ERV Plasma C_{max} and AUC under Fed and Fasted Conditions on Days 1, 3 and 7

Day	Fed				Fasted			
	Cmax (ng/mL)	AUC (ng*h/mL)			Cmax (ng/mL)	AUC (ng*h/mL)		
		0-12	12-24	0-24		0-12	12-24	0-24
1	2360 (23)	5530 (17)		7020 (17)	2280 (29)	5440 (23)		6980 (22)
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CV% - Percentage of coefficient of variation

Figure 2. Oral ERV Plasma Concentration vs. Time

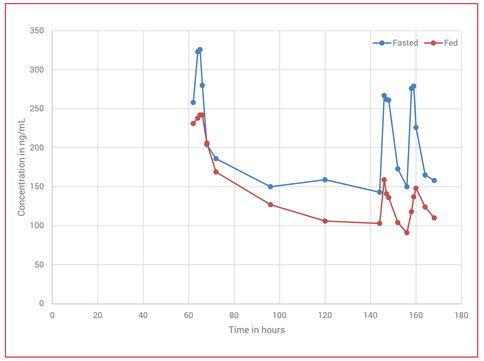
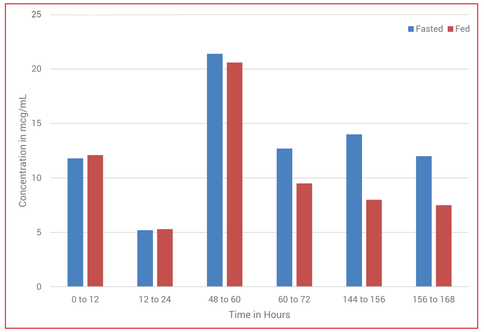


Figure 3. Urine ERV Concentrations (µg/mL) vs. Time



Safety Results

- In total, 12 of 16 (75.0%) subjects had a treatment-emergent adverse event (TEAE), which were mild in severity and considered to be study drug related.
- The most commonly reported TEAEs were nausea, vomiting, diarrhea and infusion site erythema, all of which occurred at rates similar to those observed in previous phase 1 studies with eravacycline.
- There was a higher incidence of gastrointestinal TEAEs for subjects who were fasted than for subjects who were fed.
- No deaths or serious AEs occurred during the study. No discontinuations were due to TEAE.

Conclusions

- The data from this current study support IGNITE2 study analyses and demonstrate that the meal and dosing schedule resulted in potentially non-therapeutic ERV exposures levels.
- The exposures and urine concentrations observed with IV ERV in the fasted arm are well within the expected therapeutic range and support the efficacy of IV ERV in the treatment of cUTI.
- Study results show that ERV administered orally under fasted conditions offers higher oral bioavailability than when administered under the meal and dosing schedule used in the previous phase 3 study. Therefore, it is likely that a meal and dosing schedule can be designed that will provide therapeutic ERV exposures during oral dosing.

References

1. Tsai L, Zervos M, Miller L, et al. 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). Poster presented at: ASM Microbe; 2016 Jun 16 - 20; Boston, MA.
2. Tsai L, Das A, Mohr J, et al. Risk Factors for Change in Outcome Between the End of Therapy (EOT) and Post-Treatment (PT) Evaluations in Patients with Complicated Urinary Tract Infections (cUTI) Treated with Eravacycline (ERV): Analysis from a Randomized, Double Blind, Phase 3 Trial (IGNITE2). Poster presented at: ASM Microbe; 2016 Jun 16 - 20; Boston, MA.
3. Tsai L, Zervos M, Miller L, et al. 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). Poster presented at: ASM Microbe; 2016 Jun 16 - 20; Boston, MA.