Poster 2107

23rd ECCMID
Berlin, Germany
27-30 April, 2013

Time to Defervescence as an Early Marker of Clinical Response in Patients with Complicated Intra-abdominal Infections Treated with Eravacycline or Ertapenem

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Abstract

Objectives: Early markers for clinical response are becoming increasingly utilized as outcome measures in studies of infected patients. We investigated time to defervescence in a recently completed randomized, double-blind, multicenter phase 2 study evaluating the efficacy and safety of eravacycline (TP-434) at 1.5 mg/kg q24h (ERV 1.5) and 1.0 mg/kg q12h (ERV 1.0) compared to ertapenem 1.0 g q24h (Erta) in the treatment of complicated intra-abdominal infection (cIAI).

Methods: This exploratory analysis included only subjects who were febrile (>38.0°C) at baseline. Time to defervescence was defined as the first time that a subject's temperature was ≤ 38.0°C for all evaluations over the following 24-hour period. Subjects who did not have 24 hours of data to determine if defervescence was achieved and subjects who discontinued treatment with study drug prior to attaining defervescence were censored at the last evaluation at which the temperature was >38.0°C.

Results: 143 subjects meeting the study's inclusion criteria were enrolled; 74 met the criteria for this evaluation, 27, 30, and 17 in the ERV 1.5, ERV 1.0, and Erta arms, respectively.

Time to defervescence is displayed graphically by using Kaplan Meier methodology for the MITT population below. 88.9%, 96.7%, and 100% of subjects in the ERV 1.5, ERV 1.0, and Erta groups, respectively achieved defervescence. There were more subjects with censored data in the ERV 1.5 group (11.1%) than in the ERV 1.0 (3.3%) and Erta (0%) groups. The estimated median time to defervescence in hours was lower in the ERV 1.0 group (15.7 hours) followed by the Erta group (31.3 hours) and the ERV 1.5 group (60.0 hours). The interquartile range in hours was similar for the TP 1.0 (9.0, 58.5) and Erta (7.6, 58.5) groups. The P value of the pairwise comparison between ERV 1.5 and Erta was 0.086, and the P value of the pairwise comparison between ERV 1.0 and Erta was 0.824.

Conclusions: This exploratory analysis supports the primary and secondary analyses in the study which demonstrated similar efficacy of both eravacycline arms and the ertapenem arm. Upon confirmation, it also supports the use of time to defervescence as an early marker of clinical response in patients being treated for cIAI.

Introduction

In a recent Phase 2 study (**1**) in subjects with complicated intra-abdominal infections (cIAI), safety and efficacy of two doses of intravenous eravacycline (ERV, 1.5 mg/kg q24h and 1.0 mg/kg q12h) were compared to ertapenem (Erta, 1.0 g q24h). The primary efficacy analysis was clinical response at the test of cure visit (approximately 14 days after completion of therapy) in the microbiologically evaluable population. Primary efficacy results are shown in Table 1.

Table 1: Clinical Response at Test of Cure Visit Microbiologically Evaluable Population

Study Drug	Cure	95% CI
ERV 1.5 mg/kg q24h	92.9%	(80.5 - 98.5%)
ERV 1.0 mg/kg q12h	100%	(91.4 - 100%)
Erta 1.0 g q24h	92.3%	(74.9 – 99.1%)

In this study, 143 subjects were randomized and 139 received study drug and were included in the MITT population. This poster presents results of a pre-defined exploratory efficacy analysis that looked at the time to defervescence in the MITT population as an early indicator of clinical response

Methods

- Subjects in the MITT population who were febrile at baseline (temp > 38.0°C) were included in this analysis.
- Time of defervescence was defined as the first time that the temperature was ≤ 38.0°C and remained so for at least 24 hours
- Subjects were censored at the last time that the temperature was > 38.0°C if:
  - There was not 24 hours of data to determine if defervescence was achieved
  - Study drug was discontinued prior to attaining defervescence
- Time to defervescence was displayed graphically using Kaplan-Meier methodology
- The Wilcoxon (2) test was used for pairwise comparisons of the Kaplan-Meier curves between treatment groups

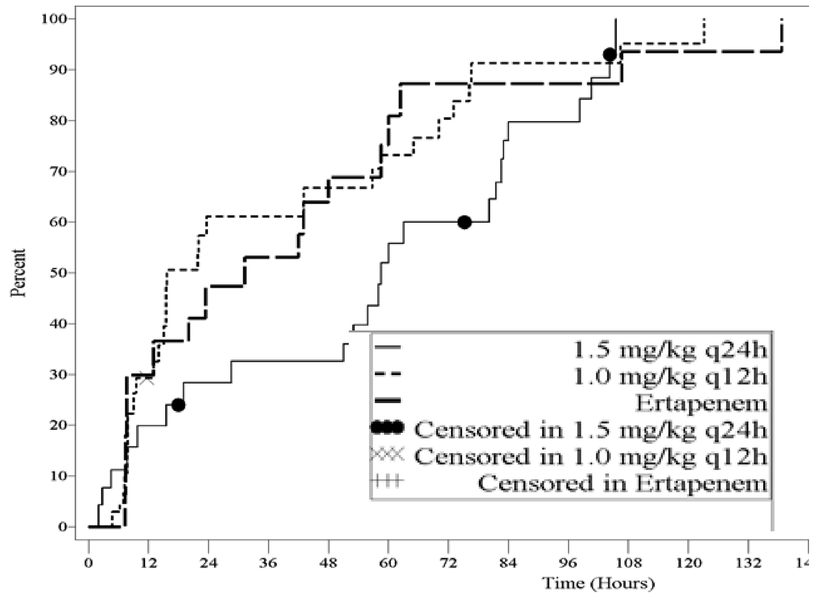
Results

Seventy-four (74) of 139 subjects (53.2%) in the MITT population were febrile at baseline and included in this analysis; 27/54 (50%), 30/56 (54%), and 17/29 (57%) in the ERV 1.5, ERV 1.0, and Erta groups, respectively. Results are shown in Table 2 and Figure 1.

Table 2: Time to Defervescence

	ERV 1.5	ERV 1.0	Erta
MITT (N)	54	56	29
Eligible for analysis (n)	27	30	17
Achieved defervescence	24 (88.9%)	29 (96.7%)	17 (100%)
Censored	3 (11.1%)	1 (3.3%)	0
Time to defervescence (h)	60.0	15.7	31.3
95%CI	(28.6, 82.6)	(13.0, 43.0)	(7.6, 138.7)
IQR	19.0, 84.0	9.0, 58.5	7.6, 58.5

Figure 1: Time to Defervescence Kaplan-Meier Plot



Pairwise Comparisons:
- ERV 1.5 v Erta p = 0.086
- ERV 1.0 v Erta p = 0.824

Conclusions

- **Clinical cure rate was similar for either dose of ERV and Erta**
- **Time to defervescence was similar for either dose of ERV and Erta**
- **For subjects with cIAI who are febrile at baseline, time to defervescence appears to be an early indicator of clinical response**

References

1 Solomkin et al. Efficacy and Safety of TP-434 (Eravacycline) versus Ertapenem in Complicated Intra-Abdominal Infection (cIAI) . Abstract L1-1647a, ICAAC 2012
2. Wilcoxon F. Individual comparisons by ranking methods. Biometrics Bulletin. 1945;1(6):80-83.