Evracynline in Complicated Intra-Abdominal Infections

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Abstract

Background: Evracynline is a novel, fully-synthetic fluorocycline antibiotic that was evaluated in three comparator-controlled studies for the treatment of complicated intra-abdominal infections (cIAI). The objective of this analysis was to evaluate the safety profile of evracynline 1 mg/kg IV q12h for the treatment of cIAI.

Methods: Pooled data from one phase 2 and two phase 3 (IGNITE1 and IGNITE4) clinical trials in cIAI were analyzed. Patients in the trials were randomized to receive evracynline 1 mg/kg IV q12h (ertapenem 1 g q24h, meropenem 1 g IV q8h for 4-14 days). Overall treatment-emergent adverse events (TEAEs), serious TEAEs, and laboratory assessments were evaluated.

Results: 576 patients were treated with evracynline 1 mg/kg IV q12h and 547 patients with comparators (ertapenem and meropenem). Demographic and baseline characteristics were similar among the groups. Overall summary and common TEAEs are presented in Table 1. None of the serious TEAEs or those leading to death were related to the study drug. Clinically notable laboratory abnormalities were relatively uncommon and occurred at similar frequencies in evracynline- and comparator-treated patients.

Table 1. Overall Summary of Treatment Emergent Adverse Events – Evracynline Phase 2 and Phase 3 Clinical Studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ertapenem (n=547)</th>
<th>Meropenem (n=547)</th>
<th>Ertapenem vs. Meropenem (n=547)</th>
<th>Meropenem vs. Ertapenem (n=547)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>3 (0.5)</td>
<td>4 (0.7)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>70 (12.9)</td>
<td>74 (13.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Treatment-related TEAE</td>
<td>217 (37.7)</td>
<td>218 (39.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Nausea</td>
<td>41 (7.5)</td>
<td>47 (8.6)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>44 (7.9)</td>
<td>41 (7.5)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Anemia</td>
<td>13 (2.4)</td>
<td>12 (2.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (1.3)</td>
<td>6 (1.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>11 (2.0)</td>
<td>12 (2.2)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Conclusion: This pooled analysis demonstrated that evracynline 1 mg/kg IV q12h was generally well tolerated for the treatment of cIAI when compared to ertapenem and meropenem. Results of the analysis are consistent with those of individual clinical studies and no new safety signals were identified.

Methods (cont’d)

Introduction

Ervacycline is a fully-synthetic fluorocycline antibacterial of the tetracycline class that has recently received Food and Drug Administration (FDA) approval for the treatment of complicated intra-abdominal infections (cIAI). Evracynline has activity against a broad range of Gram-negative, Gram-positive, and anaerobic strains.

Efficacy of evracynline for the treatment of complicated intra-abdominal infections (cIAI) was demonstrated in three controlled clinical trials: one Phase 2 and two Phase 3 clinical trials (IGNITE1 and IGNITE4). The objective of this analysis was to evaluate the safety profile of evracynline 1 mg/kg IV q12h for the treatment of cIAI by pooling safety data from the three trials.

Methods

A phase 2, randomized, double-blind, active-control study was conducted to assess the efficacy and safety of two dose regimens of evracynline (1 mg/kg IV q12h, 1.5 mg/kg IV q24h) vs. ertapenem (1 g IV q24h) in patients 18-75 years of age who had a confirmed diagnosis of cIAI that required urgent surgical or percutaneous intervention (Figure 1). Test-of-cure (TOC) evaluations occurred 10 to 14 days after the last dose of study drug. A follow-up visit occurred 28 to 42 days after the last dose of study drug.

Key Inclusion Criteria

• Male or female subjects hospitalized for cIAI
• At least 18 years of age
• Evidence of a systemic inflammatory response
• Abdominal pain or flank pain (with or without rebound tenderness), or pain associated with cIAI
• Serum creatinine clearance of ≤50 milliliter (mL)/minute (<30 mL/min for Phase 2)
• Anticipated need for systemic antibiotics for a duration of more than 48 hours

Key Exclusion Criteria

• History of moderate or severe hypersensitivity reactions to tetracyclines, carbapenems, β-lactam antibiotics, or to any of the excipients contained in the study drug formulations
• Known or suspected current central nervous system (CNS) disorder that may predispose to seizures or lower seizure threshold (for example, severe cerebral arteriosclerosis, epilepsy)
• Antibiotic-related exclusions:
  - Receipt of effective antibacterial therapy for cIAI for a continuous duration of >24 hours during the 72 hours preceding randomization
  - Receipt of ertapenem, meropenem or any other carbapenem, or tigecycline for the current infection
  - Need for concomitant systemic antimicrobial agents effective in cIAI other than study drug
  - The anticipated need for systemic antibiotics for a duration of more than 14 days (IGNITE1 and IGNITE4)
  - Known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs

Safety assessment included adverse events, laboratory tests, vital signs, electrocardiograms, and physical examinations. The safety population included all randomized patients who received any amount of study drug.

Results (cont’d)

• A total of 576 patients treated with evracynline 1 mg/kg IV q12h and 547 patients treated with comparators were evaluated for adverse events (Table 1). The median age of patients treated with evracynline was 54 years (range 18-93); 28.3% were ≥ 65 years of age.

• The eravacycline treated population included 28% obese patients (BMI ≥30 kg/m2).

• The eravacycline treated population included 7.8% with baseline moderate to severe renal impairment.

• No new safety signals were identified in this pooled analysis. This pooled analysis demonstrated that eravacycline 1 mg/kg IV q12h was generally well tolerated for the treatment of cIAI when compared to ertapenem and meropenem. The primary endpoint was clinical response in the microbiological intent-to-treat (micro-ITT) population at the TOC visit, which occurred 25 to 31 days after the initial dose of study drug. The difference in clinical cure rates between treatment groups was 11% (72.6% vs. 61.9% for eravacycline vs. comparators, respectively; p=0.0003).

• The percentage of patients completing treatment with comparators was 98.5% vs. 97.9% for eravacycline (p=0.045).

• The rate of patients who discontinued due to AEs was 11% for eravacycline vs. 12% for comparators (p=0.022).

• The rate of patients who abandoned study drug due to AEs was 6% for eravacycline vs. 7% for comparators (p=0.048).

• The incidence of gastrointestinal AEs was 21.9% for eravacycline vs. 20.4% for comparators (p=0.274).

• The percentage of patients with clinical and microbiological cure was 97% for eravacycline vs. 34% for comparators (p<0.001).

Conclusions

This pooled analysis demonstrated that eravacycline 1 mg/kg IV q12h was generally well tolerated for the treatment of cIAI when compared to ertapenem and meropenem. No new safety signals were identified in this analysis, which demonstrates the consistent safety profile of evracynline.

References


