Results of IGNITE4: A Phase 3 Study to Evaluate the Efficacy and Safety of Eravacycline versus Meropenem in Complicated Intra-abdominal Infections

Larry Tsai¹, Patrick Horn¹, Joseph Solomkin², David Evans³, Janis Gardovskis⁴

¹Tetraphase Pharmaceuticals, Watertown, MA
²University of Cincinnati
³The Ohio State University
⁴P. Stradins Clinical University Hospital
Eravacycline: A Novel Fluorocycline

- Novel, fully-synthetic fluorocycline antibiotic
- Retains activity against the most common tetracycline-specific acquired resistance mechanisms (i.e., efflux and ribosomal protection)
- Eravacycline has potent activity against antibiotic-resistant bacteria identified as urgent/critical or serious/high threats by CDC and WHO, as well as certain anaerobes
  - Carbapenem-resistant Enterobacteriaceae (CRE)
  - Methicillin-resistant *Staphylococcus aureus* (MRSA)
  - Extended-spectrum beta-lactamases (ESBL)-producing Enterobacteriaceae
  - Vancomycin-resistant enterococci (VRE)
  - Multidrug-resistant (MDR) *Acinetobacter*
  - *Bacteroides fragilis*
- Eravacycline is under FDA and EMA review for indication in patients with cIAI

Bassetti et al. P1820 Presented at IDWeek, October 26-30, 2016, New Orleans, LA, USA

28th ECCMID
24-24 April, 2018 Madrid, Spain
**Study Design**

**NONINFERIORITY TRIAL**

(NI margin: 12.5%)

- **Primary Endpoint**
  - Test of Cure
  - Days 25-31
  - Days 38-50

- **POST-TREATMENT EVALUATIONS**
  - 4- to 14-Day Dosing Period

- **Treatment Groups**
  - **Eravacycline**
    - 1.0 mg/kg IV q12h
    - N = 500 (1:1)
  - **Meropenem**
    - 1.0 g IV q8h

- **Secondary Endpoints**
  - End of therapy
  - Long-term follow-up

The design of the study adhered to both the FDA and EMA development guidance.

*28th ECCMID*
24-24 April, 2018 Madrid, Spain
### Demographics and Baseline Characteristics

**MITT population**

<table>
<thead>
<tr>
<th></th>
<th>Eravacycline (N=250)</th>
<th>Meropenem (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, male, n (%)</td>
<td>139 (55.6)</td>
<td>129 (51.8)</td>
</tr>
<tr>
<td>Race, White, n (%)</td>
<td>249 (99.6)</td>
<td>249 (100)</td>
</tr>
<tr>
<td>Age, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>180 (72)</td>
<td>174 (69.9)</td>
</tr>
<tr>
<td>≥65</td>
<td>70 (28)</td>
<td>75 (30.1)</td>
</tr>
<tr>
<td>APACHE II score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>202 (80.8)</td>
<td>200 (80.3)</td>
</tr>
<tr>
<td>≥10</td>
<td>48 (19.2)</td>
<td>49 (19.7)</td>
</tr>
<tr>
<td>≥15</td>
<td>7 (2.8)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Primary Disease Diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated Appendicitis</td>
<td>99 (39.6)</td>
<td>99 (39.8)</td>
</tr>
<tr>
<td>Other cIAI</td>
<td>151 (60.4)</td>
<td>150 (60.2)</td>
</tr>
</tbody>
</table>

**MITT** = modified intent-to-treat
Baseline Pathogen Distribution

- 39% Gram-negative aerobes, 26% Gram-positive aerobes and 35% anaerobes
- 1445 baseline isolates; 3.6 isolates/patient

**GRAM-NEGATIVES**
- **E. coli**
- **K. pneumoniae**
- Other Enterobacteriaceae
- Non-Enterobacteriaceae

**ANAEROBES**
- Anaerobes

**GRAM-POSITIVES**
- **Enterococci spp**
- **Staphylococci spp**
- **Streptococci spp**
- Other Gram-positive aerobes
Efficacy Overview

Clinical Response at TOC

- **Clinical Cure Rate, %**
  - **Eravacycline**
    - micro-ITT: 90.8 (95% CI: -0.5, -6.3, 5.3)
    - MITT: 92.4 (95% CI: 0.8, -4.1, 5.8)
    - CE: 96.9 (95% CI: 0.8, -2.9, 4.5)
  - **Meropenem**
    - micro-ITT: 91.2
    - MITT: 91.6
    - CE: 96.1

**Eravacycline**

- Met FDA and EMA endpoints demonstrating non-inferiority to meropenem in cIAI patients
- Achieved high clinical cure rates

**TOC** = test of cure; **micro-ITT** = microbiological intent-to-treat; **MITT** = modified intent-to-treat; **CE** = clinically evaluable
Clinical Response per Pathogen at TOC (micro-ITT)

- E. coli (n=260)
- K. pneumoniae (n=49)
- P. aeruginosa (n=39)
- Streptococcus spp (n=110)
- Staphylococcus aureus (n=24)
- E. faecalis (n=59)
- E. faecium (n=52)
- Bacteroides spp (n=182)

Clinical Cure Rate, %

TOC = test of cure; micro-ITT = microbiological intent-to-treat
Safety Overview

<table>
<thead>
<tr>
<th>TEAEs Occurring in &gt;2% of Subjects, n (%)</th>
<th>Eravacycline (N=250)</th>
<th>Meropenem (N=249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>12 (4.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (3.6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Infusion site phlebitis</td>
<td>8 (3.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (2.4)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (1.2)</td>
<td>6 (2.4)</td>
</tr>
</tbody>
</table>

- Eravacycline was generally well-tolerated
- There were no drug-related serious adverse events

TEAE: Treatment Emergent Adverse Event