**Poster #1837**

**Safety Results from the ZEUS Study: Multi-center, Randomized, Double-Blind Phase 2/3 Study in Hospitalized Adults with Complicated Urinary Tract Infections (cUTI) Including Acute Pyelonephritis (AP) Who Received Intravenous Fosfomycin (ZTI-01)**


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Presented at ID Week, October 7, 2017, San Diego, CA

**Abstract**

**Background**

Intravenous (IV) fosfomycin (FOS) has been used systemically to treat cUTI and AP, though dosing details in adults are limited. Zavante Therapeutics, Inc. (ZTI) is developing FOS for the treatment of complicated urinary tract infections (cUTIs) and acute pyelonephritis (AP) in infections caused by resistant Gram-negative bacteria (GNB), including ESBL and CR- and MDR-Enterobacteriaceae (EBs and AEs).

**Methods**

ZTI-01 is being developed for the treatment of cUTIs and AP caused by ESBL and CR/AE. In a number of serious infections (including cUTIs), efficacy and safety of IV fosfomycin has been established after >45 years of use in more than 60 clinical studies. New therapeutic options with different mechanisms of action and established safety are desperately needed in the USA. (Table 1). The next-generation FOS derivative, ZTI-01, is being developed for the treatment of cUTIs and AP and was performed on day 28.

**Results**

Safety and tolerance are being evaluated, including adverse events (AEs), risk signs, laboratory assessments and fluid balance assessments, serum potassium monitoring, and utilization of potassium supplementation.

**Conclusion**

ZTI-01 is associated with a higher incidence of liver transaminase elevations compared with P. The pattern of ALT/AST elevation in the ZTI was predominantly hepatocellular or mixed hepatic injury, and reversible based on blinded adjudication. Gastrointestinal events were the most common symptomatic clinical AEs. The ZTI is well-tolerated in patients with cUTI and AP. (Table 2). In the ZTI group, mild severity, >10x ULN

**Keywords**

Intravenous fosfomycin; AP; cUTI; safety; ZTI-01; treatment emergent adverse events; N=231

**Figures 1. Study Design**

**Table 1. Basic Demographics for ZTI-01 (N=233) and P. (N=233)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ZTI-01 (n=233)</th>
<th>P (n=233)</th>
<th>P vs. ZTI-01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53.4 (18.1)</td>
<td>53.5 (16.2)</td>
<td>NS*</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>222 (47.8%)</td>
<td>208 (44.8%)</td>
<td>NS*</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>176 (38.0%)</td>
<td>172 (37.3%)</td>
<td>NS*</td>
</tr>
<tr>
<td>Discordance on ASB, n (%)</td>
<td>79 (17.2%)</td>
<td>77 (16.8%)</td>
<td>NS*</td>
</tr>
<tr>
<td>NAU, n (%)</td>
<td>172 (38.0%)</td>
<td>169 (37.5%)</td>
<td>NS*</td>
</tr>
<tr>
<td>MDR NAB, n (%)</td>
<td>169 (37.5%)</td>
<td>166 (36.1%)</td>
<td>NS*</td>
</tr>
</tbody>
</table>

**Table 2. Adverse Events (WITT Safety Population)**

- **Non-Severe AEs:**
- **Severe AEs:**

**Table 3. TEAEs (≥3%) in System Organ Class (WITT Safety Population)**

- **System Organ Class, n (%)**
- **ZTI-01 (n=233) | P (n=233) | ZTI-01 vs. P**

**Table 4. Incidence of TEAEs that Occur ≥2% of Patients (any treatment) (WITT Safety Population)**

**Table 5. Frequency of Highest Transaminase Value at Any Post-Treatment Evaluation (N=231)**

- **Parameter**
- **ALT (IU/L) vs. ULN**
- **AST (IU/L) vs. ULN**

**Table 6. Severity of Hypophosphatemia and Hypokalemia Based on Worst Post-Treatment Evaluation (N=231)**

- **Parameter**
- **Hypophosphatemia (≤2 mg/dL) vs. ≤4 mg/dL**
- **Hypokalemia (≤2 mmol/L) vs. ≤3 mmol/L**

**Conclusions**

- If fosfomycin has been used safely outside the USA for 50 years, doses used are the same as used in USA in a variety of serious infections.
- In the Phase 2/3 cUTI study, ZTI-01 (18 g/day) was well-tolerated.

**References**

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