The Lack of Effect of Food on the Pharmacokinetics of ZX008 (Fenfluramine Oral Solution): Results of a Single-Dose, Two-Period Cross-Over Study

INTRODUCTION

Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) are Ratio (%)

Key inclusion criteria

1. Patients

2. Sex, n (%)

3. Age, y, mean±SD (range)

4. Body mass index (BMI), kg/m²

5. Clinical history

6. Other

Pharmacokinetics: FFA

FFA, the active drug, was quantifiable up to 72 hours post-dose in all subjects, with both fasted and fed states. Plasma terminal half-lives were comparable in all subjects, resulting in terminal half-lives (t1/2) ranging from 15.8-22.7 hours.

Pharmacokinetics: NorFFA

NorFFA concentrations were quantifiable to 72 hours under both dietary conditions. No difference in NorFFA levels resulted in comparable median terminal half-lives in fasted and fed subjects.

Figure 2. Plasma concentration vs time for norFFA.

Pharmacokinetic Evaluations

Venous blood samples were taken before each dose and at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72 hours following each administration of ZX008.

FFA and norFFA plasma concentrations were determined by ICAS Biological Services (Shrewsbury, KS, USA) using a validated bioanalytical method (lower limit of quantification: 0.25 ng/mL).

Panel PK parameters were estimated by noncompartmental analysis using Phoenix WinNonlin v.3.3 (Certara, Princeton, NJ, USA).

Plasma PK parameters were estimated by noncompartmental analysis using Phoenix WinNonlin v.3.3 (Certara, Princeton, NJ, USA).

$\text{t}_1/2$ - terminal half-life

$\text{C}_{\text{max}}$ - maximum observed plasma concentration

$\text{AUC}_{0-t}$ - area under the curve from 0 time to the last measurable concentration

$\text{AUC}_{0-\infty}$ - area under the curve from 0 time to infinity

$\text{t}_{\text{max}}$ - the terminal elimination half-life

$\text{CL/F}$ - clearance

$\text{V}_{\text{d,ss}}$ - apparent volume of distribution

$\text{t}_{\text{lag}}$ - time from dosing to $\text{C}_{\text{max}}$

$\text{C}_{\text{max},\text{fed/fasted}}$ - maximum observed plasma concentration in the fed and fasted states

$\text{AUC}_{0-\text{fed/fasted}}$ - area under the curve from 0 time to infinity in the fed and fasted states

$\text{C}_{\text{max},\text{fed/fasted}}$, $\text{AUC}_{0-\text{fed/fasted}}$ values are median (range), remaining parameter values are mean±SD.

Bioequivalence Analysis for FFA

The presence of food had no effect on FFA rate or extent of absorption. The data met bioequivalence criteria (ie, 90% Cs of geometric mean ratio (GMR) of fasted conditions were completely contained within 80%-125%) after a single dose of 0.8 mg/kg ZX008 (Table 2).

Table 2. Key Pharmacokinetic Parameters for FFA

<table>
<thead>
<tr>
<th>Measured Agent</th>
<th>n</th>
<th>$\text{C}_{\text{max},\text{fed/fasted}}$ (ng/mL)</th>
<th>$\text{AUC}_{0-\text{fed/fasted}}$ (ng·h/mL)</th>
<th>$\text{t}_{\text{lag}}$ (h)</th>
<th>$\text{t}_{\text{max}}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA: Fasted</td>
<td>14</td>
<td>3.0 (1.5-4.0)</td>
<td>37.25±10.1</td>
<td>0.25</td>
<td>21.2±3.6</td>
</tr>
<tr>
<td>FFA: Fed</td>
<td>14</td>
<td>3.0 (1.5-4.0)</td>
<td>37.25±10.1</td>
<td>0.25</td>
<td>21.2±3.6</td>
</tr>
</tbody>
</table>

Table 3. Statistical Analysis of FFA Bioavailability

<table>
<thead>
<tr>
<th>Treatment*</th>
<th>Fasting*</th>
<th>Ratio*</th>
<th>CIs*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasted</td>
<td>34.0±9.7</td>
<td>1.00</td>
<td>0.66-1.5</td>
</tr>
<tr>
<td>Fed</td>
<td>34.0±9.7</td>
<td>1.00</td>
<td>0.66-1.5</td>
</tr>
</tbody>
</table>

Plasma norFFA (ng/mL) - Fasted

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Plasma norFFA (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>0.25</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>0.5</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>1</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>3</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>6</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>24</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>48</td>
<td>0.56 (0.39-0.80)</td>
</tr>
<tr>
<td>72</td>
<td>0.56 (0.39-0.80)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

Food had no effect on the rate or extent of absorption of FFA nor on the systemic exposure of FFA after a single dose of 0.8 mg/kg of ZX008.

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REFERENCES


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DISCLOSURE