A Phase 1, Single-Dose, Open-Label Pharmacokinetic Study to Investigate the Drug-Drug Interaction Potential of ZX008 (Fenfluramine HCl Oral Solution) and Cannabidiol

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Introduction

Adverse fenfluramine (FFA, administered as an oral solution of fenfluramine HCl containing 23 mg/kg fenfluramine) demonstrated predictable efficacy with low (0.35 mg/kg) dosing for treatment of Lennox-Gastaut Syndrome (LGS) in Phase 2 clinical trials. Concomitant use has been shown in vitro to:

- Increase CYP3A4 activity
- Decrease CYP2B6 activity
- Inhibit CYP2A6 activity

While these interactions do not cause significant changes in phenytoin concentrations, inhibition of CYP2B6 may impact barbiturate or valproate concentrations.

Methods

This study was a single-center, Phase 1, open-label, single-dose, fixed-dose, sequential, 2-stage, 2-sequence, single-center, single-dose study to investigate the pharmacokinetics of FFA and cannabidiol (CBD) alone and co-administered at steady-state, with pharmacokinetic follow-up. The study enrolled healthy adult recreational drug users with recent cannabis product experience in order to minimize the potential impact by the psychoactive THC component of the CBD product.

The study was a Phase 1, single-center (Canada), 1-sequence, single-dose drug-drug interaction study to evaluate the impact of CBD on FFA pharmacokinetics following a single dose of FFA oral solution (0.35 mg/kg), with and without steady-state CBD administration.

Objectives

To determine the safety, tolerability, pharmacokinetics of FFA and CBD alone, and co-administered at steady-state.

Results

Table 1: Participant Disposition and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FFA-alone (n=14)</th>
<th>CBD-alone (n=14)</th>
<th>Total (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>10/4</td>
<td>10/4</td>
<td>20/8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>25±3 (20-30)</td>
<td>25±3 (20-30)</td>
<td>25±3 (20-30)</td>
</tr>
</tbody>
</table>

Table 2: Primary PK Parameters for FFA and norFFA After FFA-CBD Administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>FFA-alone (n=14)</th>
<th>CBD-alone (n=14)</th>
<th>Total (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mL)</td>
<td>581±123 (322-803)</td>
<td>528±112 (299-734)</td>
<td>555±119 (322-803)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>244±62 (140-348)</td>
<td>224±52 (120-315)</td>
<td>234±55 (140-348)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.5±0.5</td>
<td>0.5±0.5</td>
<td>0.5±0.5</td>
</tr>
</tbody>
</table>

Table 3: Key CBDO Parameters for CBD-Only

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CBD-only (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (ng/mL)</td>
<td>131±25 (77-183)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>308±63 (180-433)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>0.5±0.5</td>
</tr>
</tbody>
</table>

Table 4: TEAEs Occurring in ≥10% of Participants at Any Treatment Level

<table>
<thead>
<tr>
<th>TEAE</th>
<th>FFA-alone (n=14)</th>
<th>CBD-alone (n=14)</th>
<th>Total (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoric mood</td>
<td>100%</td>
<td>57%</td>
<td>73%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>57%</td>
<td>57%</td>
<td>57%</td>
</tr>
<tr>
<td>Tetany</td>
<td>43%</td>
<td>43%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Table 5: Key GMRs for CBD-Only

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.85 (0.70-1.04)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.88 (0.74-1.05)</td>
</tr>
</tbody>
</table>

Table 6: Key GMRs for CBD-FFA or norFFA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>0.85 (0.70-1.04)</td>
</tr>
<tr>
<td>Cmax</td>
<td>0.88 (0.74-1.05)</td>
</tr>
</tbody>
</table>

Conclusions

- FFA steady-state mean AUC120 was 0.58 ng·h/mL, consistent with FFA's exposure for a single dose of 0.35 mg/kg (90% CI). The maximum observed dose of the FFA-approved product (ZyloFen®) is 3 mg/kg.
- FFA was not expected to interfere with FFA study objectives (analysis for THC, 1-OH-THC not shown).
- Most TEAEs were mild (78%) or moderate (22%) in severity.
- Two serious adverse events of drug-related psychoses were considered to be related to 300 mg CBD: 100 mg CBDO.
- In an open-label, investigator-initiated study in patients with LGS, FFA treatment resulted in a 53% reduction in seizure frequency.

References


Disclosures

This study was funded by the Zogenix, Inc. The authors declare no conflicts of interest.

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