Fenfluramine HCl Significantly Reduces Frequency of Generalized Tonic-Clonic Seizures in Dravet Syndrome: Pooled Analysis From Two Phase 3 Clinical Trials

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Introduction

- Dravet syndrome is a severe, treatment refractory developmental epileptic encephalopathy in which generalized tonic-clonic seizures are a common seizure type often refractory to treatment.
- Generalized tonic-clonic seizures (GTCS) are associated with elevated disease-specific mortality, most commonly due to sudden unexpected death in epilepsy (SUDEP) or status epilepticus.
- Dravet syndrome has a genetic basis in 43% per 100 years of observation.1
- ≥14 hours per week in the general population of people with epilepsy.2

- Generalized tonic-clonic seizures are a major risk factor for SUDEP.5
- This post-hoc analysis explored the impact of fenfluramine on generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures in patients enrolled in two Phase 3 clinical trials of fenfluramine added to current antiepileptic drug regimens.

Methods

- Patients with Dravet syndrome aged 2-18 years enrolled in 1 of 2 randomized, placebo-controlled clinical trials of fenfluramine were included.6
- Eligible patients were randomized to placebo or fenfluramine at 0.2 or 0.7 mg/kg/day (maximum daily dose of 26 mg/day) in patients not currently receiving stiripentol, or fenfluramine at 0.4 mg/kg/day (maximum daily dose of 17 mg/day) in patients also treated with stiripentol.
- Fenfluramine was administered as an oral solution of fenfluramine HCl containing 2.2 mg/mL fenfluramine.
- An electronic diary was used to capture seizure frequency.
- Patients with Dravet syndrome experience elevated disease-specific mortality, most commonly due to sudden unexpected death in epilepsy (SUDEP).3
- This post-hoc analysis explored the impact of fenfluramine on generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures in patients enrolled in two Phase 3 clinical trials of fenfluramine added to current antiepileptic drug regimens.

Results

- 206 patients were enrolled and randomized to placebo (n=84) or fenfluramine 0.2 mg/kg/day (n=39), 0.4 mg/kg/day (n=43), or 0.7 mg/kg/day (n=43).
- Baseline patient characteristics are shown in Table 1.

- Due to privacy laws in Europe many patients did not report race.

Conclusions

- Fenfluramine provided clinically meaningful (≥50%) and profound (≥75%) reductions in the frequency of generalized tonic-clonic and focal-to-bilateral tonic-clonic seizures in patients with Dravet syndrome.
- Fenfluramine may represent an important, effective new treatment option for patients with Dravet syndrome.

References

Disclosures
- ARG, GMF, AM, BSG, GM: Employees, Zogenix; Ownership interest, Zogenix.
- KR: Research funding, Zogenix.
- DB: Research funding, Zogenix.
- ARG, GMF, AM, BSG, GM: Ownership interest, Zogenix.

Table 1. Patient Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Age (years)</th>
<th>Gender</th>
<th>Race, n (%)</th>
<th>Race</th>
<th>Median (min, max)</th>
<th>Median (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA 0.2 mg/kg/day + STP</td>
<td>39</td>
<td>6</td>
<td>Male</td>
<td>20 (17-99)</td>
<td>80.6 (4.8-100)</td>
<td>52 (17-99)</td>
<td></td>
</tr>
<tr>
<td>FFA 0.4 mg/kg/day + STP</td>
<td>31</td>
<td>6</td>
<td>Male</td>
<td>20 (17-99)</td>
<td>80.6 (4.8-100)</td>
<td>52 (17-99)</td>
<td></td>
</tr>
<tr>
<td>FFA 0.7 mg/kg/day + STP</td>
<td>11</td>
<td>6</td>
<td>Male</td>
<td>20 (17-99)</td>
<td>80.6 (4.8-100)</td>
<td>52 (17-99)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Treatment-Emergent Adverse Events Occurring in ≥10% of Patients in Any Treatment Group

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Decreased appetite</th>
<th>Fatigue</th>
<th>Gastrointestinal disturbance</th>
<th>Somnolence</th>
<th>Lethargy</th>
<th>Decreased appetite</th>
<th>Fatigue</th>
<th>Gastrointestinal disturbance</th>
<th>Somnolence</th>
<th>Lethargy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA 0.2 mg/kg/day + STP</td>
<td>39</td>
<td>8 (20.5)</td>
<td>17 (43.6)</td>
<td>14 (35.9)</td>
<td>20 (51.3)</td>
<td>12 (30.8)</td>
<td>7 (17.9)</td>
<td>17 (43.6)</td>
<td>14 (35.9)</td>
<td>20 (51.3)</td>
<td>12 (30.8)</td>
</tr>
<tr>
<td>FFA 0.4 mg/kg/day + STP</td>
<td>31</td>
<td>8 (26.2)</td>
<td>2 (6.5)</td>
<td>1 (3.2)</td>
<td>3 (9.7)</td>
<td>1 (3.2)</td>
<td>2 (6.5)</td>
<td>1 (3.2)</td>
<td>3 (9.7)</td>
<td>1 (3.2)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>FFA 0.7 mg/kg/day + STP</td>
<td>11</td>
<td>8 (72.7)</td>
<td>5 (45.5)</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>5 (45.5)</td>
<td>1 (9.1)</td>
<td>2 (18.2)</td>
<td>1 (9.1)</td>
<td>5 (45.5)</td>
</tr>
</tbody>
</table>

Figure 1. Effect of FFA on the frequency of generalized tonic-clonic seizures in patients with Dravet syndrome

Figure 2. Effect of FFA on the frequency of focal-to-bilateral tonic-clonic seizures in patients with Dravet syndrome

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