Add-on Therapy with Low Dose Fenfluramine (ZX008) in Lennox Gastaut Syndrome

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METHODS

Fenfluramine (FFA)

INTRODUCTION

An efficacy response was defined as a ≥50% reduction in major motor seizure frequency between the visits at week 12 and week 16 in the trial. 7 of the 13 patients (54%) achieved at least a 50% reduction in the number of major motor seizures. There was approximately a 2-fold increase in the number of responders (≥50% reduction) on a dose of 0.4 mg/kg/day vs. 0.2 mg/kg/day (Figure 2).

RESULTS

Demographics

Individual patient demographics are provided in Table 1. 13 patients were enrolled at the time of this interim report:

- Mean age in years (±SD): 11.4 (±4.4)
- 69% male
- Mean weight in kg (±SD): 45.4 (±20.2)

Subject disposition

4 patients withdrew before end of study at 2 weeks:

- 1 experienced worsening of seizures following orthopedic surgery
- 1 insomnia
- 8 patients completed all 20 weeks of the treatment period

Patients had received a median of 5 failed antiepileptic therapies (range: 3-7) prior to this study (Table 1).

Table 1. Dose and Time on Effective Dose

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Dose (mg/kg/day)</th>
<th>Start Date (dd/mm/yy)</th>
<th>Start Age (years)</th>
<th>Start Weight (kg)</th>
<th>Time on Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>0.2</td>
<td>3/09/04</td>
<td>11</td>
<td>35</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0.4</td>
<td>9/04/04</td>
<td>13</td>
<td>35</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Patient 3</td>
<td>0.2</td>
<td>9/04/04</td>
<td>13</td>
<td>15</td>
<td>16 weeks</td>
</tr>
</tbody>
</table>

In the intent-to-treat (ITT) patient population (n=13) there was a median reduction in seizure frequency over the 20-week study period compared to baseline (range: +74% to –90%) – the subject with a 74% increase had been a responder at 0.4 mg/kg/day (61% reduction in major motor seizure frequency at week 12 but lost control after undergoing orthopedic surgery between the visits of week 12 and week 16 in the trial).

CONCLUSIONS

In this pilot study evaluating ZX008 for the treatment of uncontrollable seizures in LGS, interim results (n=13) after at least 12 weeks of treatment suggest that ZX008 provides clinically meaningful improvement in major motor seizure frequency in patients with severely refractory LGS, despite not attempting to dose to maximal efficacy and is generally well tolerated. 71% patients (9/13) achieved a ≥50% reduction in the number of major motor seizures (range: 50%–90%) – in responders (patients with a ≥50% decrease in major motor seizures), efficacy was apparent by 4–8 weeks of treatment at the effective dose level.

In this open-label dose-finding pilot study, submaximal doses of FFA 0.2 and 0.4 mg/kg/day provided a ≥50% reduction in major motor seizures in 54% of patients. Greater seizure reductions might be seen at higher doses of FFA.

Patients in this study who are responders will be invited to enter a long-term extension study where doses will be further titrated to 0.8 mg/kg/day (with a maximum of 20 mg/day) in order to assess maximal efficacious dose.

REFERENCES


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