Introduction

Two prior clinical studies of add-on fenfluramine (FFA) in patients with Dravet syndrome (DS) showed statistically significant reduction of monthly convulsive seizure frequency (MCSF) – a primary efficacy endpoint – for the 4-week period compared to placebo. In those trials, patients were randomized to placebo (P) or fenfluramine 0.2 mg/kg/day (FFA 0.2 mg/kg/day) or fenfluramine 0.7 mg/kg/day (FFA 0.7 mg/kg/day) with a 6-week baseline period. Given the variability in seizure presentation in DS, P 2018, stiripentol and cannabidiol were approved in the US for the treatment of DS. In 2018, two phase 3 clinical studies of add-on fenfluramine (FFA) in patients with Dravet Syndrome were conducted: one with a 6-week baseline period and another with a 4-week baseline period. The shorter duration was designed to allow a more rapid determination of efficacy and was motivated by prior experience and data indicating that higher variability in assessments of change from baseline. The overall baseline design and titration strategy were carried forward from the prior studies (FFA 0.2 mg/kg/day). In 2018, stiripentol and cannabidiol were approved in the US for the treatment of DS. In 2018, two phase 3 clinical studies of add-on fenfluramine (FFA) in patients with Dravet Syndrome were conducted: one with a 6-week baseline period and another with a 4-week baseline period. The shorter duration was designed to allow a more rapid determination of efficacy and was motivated by prior experience and data indicating that higher variability in assessments of change from baseline. The overall baseline design and titration strategy were carried forward from the prior studies (FFA 0.2 mg/kg/day). In 2018, stiripentol and cannabidiol were approved in the US for the treatment of DS. In 2018, two phase 3 clinical studies of add-on fenfluramine (FFA) in patients with Dravet Syndrome were conducted: one with a 6-week baseline period and another with a 4-week baseline period. The shorter duration was designed to allow a more rapid determination of efficacy and was motivated by prior experience and data indicating that higher variability in assessments of change from baseline. The overall baseline design and titration strategy were carried forward from the prior studies (FFA 0.2 mg/kg/day).

Objective

To assess the impact of shortening the baseline period from the prior studies by using a 4-week baseline period with FFA placebo to placebo in change from baseline in MCSF.

Methods

Study Design

- Data were from Study 1, a phase 2, randomized, placebo-controlled, double-blind, 6-week add-on study comparing FFA 0.2 mg/kg/day with placebo. Patients were randomized in a 1:1:1 ratio to twice-daily add-on FFA 0.2 mg/kg/day or placebo (P).
- Patients were randomized in a 1:1:1 ratio to twice-daily add-on FFA 0.2 mg/kg/day or placebo (P).
- A blinded independent data monitoring committee (IDMC) reviewed data periodically, and FFA was administrated as XOFXO, on oral solution of FFA hydrochloride, until the end of Study 1.

Efficacy Endpoints

- Treatment groups were compared on median change in MCSF after 4 weeks (Endpoints were evaluated using either a 6-week or 4-week baseline period).
- The primary efficacy endpoint was the change in monthly convulsive seizure frequency (MCSF) from baseline to the combined Titration (T) and Maintenance (M) periods (Figure 1). The secondary efficacy endpoint was the proportion of patients with ≥25%, ≥50%, or ≥75% reduction from baseline in MCSF after FFA compared to placebo was comparable within the 6-week baseline period. In addition, the placebo group was shown to experience a US$2.2 mg/mL FFA containing 2.2 mg/mL FFA.

Table 1. Paired T-Test for Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>FFA 0.2 mg/kg/day</th>
<th>FFA 0.7 mg/kg/day</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.5 (±1.0)</td>
<td>1.5 (±1.0)</td>
<td>1.5 (±1.0)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td>51%</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>Gender (%)</td>
<td>67%</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>Duration of DS (years)</td>
<td>2.7 (±2.0)</td>
<td>2.7 (±2.0)</td>
<td>2.7 (±2.0)</td>
</tr>
<tr>
<td>Baseline CS frequency</td>
<td>19.3 ±5.7</td>
<td>22.0 ±6.9</td>
<td>22.0 ±6.9</td>
</tr>
</tbody>
</table>

Conclusions

- The re-analysis of the results using a 4-week vs 6-week baseline period: did not affect the conclusions or the statistical significance of the clinical outcomes in the primary and secondary outcomes.

Results

- A total of 197 patients with DS were randomized to treatment (n=60, 0.7 mg/kg/day FFA, n=39, 4-wk BL). Re-analysis of the results assuming a 4- vs 6-week baseline period:
- The primary efficacy endpoint was the change in monthly convulsive seizure frequency (MCSF) from baseline to the combined Titration (T) and Maintenance (M) periods (Figure 1).

References

- Joseph Sullivan, Glenn Morrison, Michael Locks, Gall M. Farfel
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Disclosures

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