Defining a Clinically Meaningful Difference in Seizure Frequency Using Data From a Phase 3 Clinical Study of Add-On, Low–Dose ZX008 (Fenfluramine HCl Oral Solution) in Dravet Syndrome Patients Receiving an Antiepileptic Drug Regimen Containing Stiripentol

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Introduction

In clinical trials, an antiepileptic drug (AED) is conventionally considered to have clinically meaningful efficacy if patients in the study population show a ≥30% reduction in seizure frequency. Yet this threshold is largely derived from observation without formal hypothesis testing in a controlled clinical trial setting.

A clinically meaningful change is difficult to determine quantitatively and tends to vary among patients based on seizure frequency reduction and levels of seizure reduction.

The minimal clinically important difference (MCID) of a given therapy can be determined using anchor- and distribution-based methodologies.

Objective

To define a clinically meaningful change in monthly seizure frequency (MSF) to better understand how to interpret data from a clinical study in patients with treatment-refractory Dravet syndrome (DS) receiving fenfluramine (FFA) added to an AED regimen containing stiripentol (STP).

Methods

Primary Data

Post-hoc analysis of data from Study 1 (NCT02940046):

- Randomized, Phase 3, double-blind, placebo-controlled trial of 87 patients with DS
- Oral administration of FFA to placebo, maximum dose of 17 mg administered as an oral solution at 3 times/day
- All patients were on an STP–inclusive AED regimen with stable seizure control
- Clinical endpoint: investigator and caregiver-rated change on the Clinical Global Impression of Improvement (CGI-I) scale
- ≥2: "Very Much Improved" vs >2 ("Minimally Improved" or Worse) After 14 Weeks of FFA Treatment

Results

Patients

A total of 82 patients had corresponding percentage MSF and CGI-I ratings for both caregivers and investigators and were included in the analysis.

Table 1. ROC Analysis

<table>
<thead>
<tr>
<th>CGI-I Category</th>
<th>Change in MSF (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Concordant (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0-24</td>
<td>45.0</td>
<td>82.7</td>
<td>69.5</td>
</tr>
<tr>
<td>FFA</td>
<td>0-24</td>
<td>53.5</td>
<td>72.5</td>
<td>73.0</td>
</tr>
</tbody>
</table>

The clinically meaningful threshold was defined as the endpoint for which specificity = sensitivity.

Figure 1: Change in MSF From Baseline to End of Study by CGI-I Categories (N=82)

Figure 2: ROC Curve Percent Change in MSF Related to CGI-I (Caregiver) and CGI-I (Investigator) for ≥37.5% "Much Improved" or Placebo vs ≥2 "Minimally Improved" or Worse After 14 Weeks of FFA Treatment

Figure 3: Response Analysis Applying the ROC-Derived MCID Threshold (≥37.5%)

Figure 4: Box Plot of Change in Seizure Frequency for Placebo and FFA across 14 Weeks

Conclusions

A threshold of ≥37.5% reduction in seizure frequency was associated with a rating of "Much Improved" or "Very Much Improved" on both investigator and caregiver CGI-I assessments.

The clinically meaningful threshold of seizure control was concordant among physicians and caregivers.

This threshold is lower than the conventionally accepted 50% threshold used by regulatory agencies and widely accepted as a threshold for meaningful seizure improvement.

It is slightly lower than the 44% reduction reported in a study of patients administered FFA with STP-free AED regimens (Study 2).

Agreement between physicians and caregivers regarding the need and expectations of families of patients receiving STP–inclusive AED regimens as compared with those not on STP regimen.

Further analyses are needed to:

- Confirm the present findings in clinical studies of additional AED combinations in patients with DS and/or other treatment-refractory seizure conditions that substantially affect patients' quality of life.
- Identify other potential factors that have an impact on caregivers and/or other treatment-refractory seizure conditions that substantially affect patients' quality of life.
- Address outcomes on disease comorbidities and drug tolerability.

References


Disclosures

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