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Defining a Minimal Clinically Important 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

ZOGENIX

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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 ≥50% reduction in seizure frequency,[1] but 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 type, reduction in severity, and level of seizure reduction
- The minimal clinically important difference (MCID) of a given therapy can be determined using anchor- and distribution-based methodologies[2,3]

Objective

- To define a clinically meaningful change in monthly convulsive seizure frequency (MCSF) vs baseline using 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 1504 (NCT02926898)
  - Randomized, Phase 3 double-blind, placebo-controlled trial of 87 patients with DS
  - Oral adjunctive FFA (0.4 mg/kg/day; maximum daily dose, 17 mg) administered as an oral solution of FFA HCl[4]
  - All patients were on an STP-inclusive AED regimen with clobazam and/or valproate
- Clinical instrument: investigator and caregiver ratings on the Clinical Global Impression of Improvement (CGI-I) scale
  - 7-point Likert scale with responses ranging from 1 ("Very Much Improved") to 7 ("Very Much Worse") relative to Time 0
  - Clinically meaningful responses: 1 ("Very Much Improved") or 2 ("Much Improved")

Statistical Analysis[2]

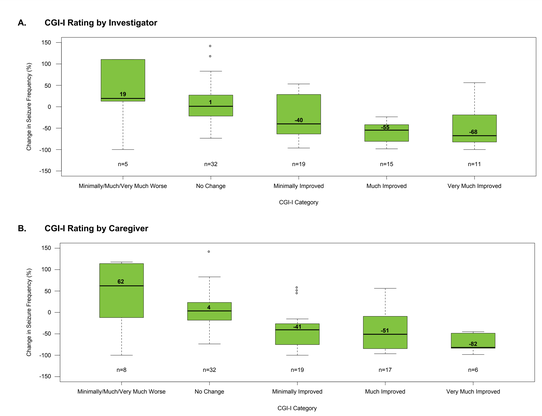
- The strength of the association between change in MCSF and CGI-I score for individual patients was assessed
- Receiver operator characteristic (ROC) analysis
  - Independent variable: percent change in seizure frequency per 28 days between baseline and the end of the combined titration and maintenance periods
  - Dependent variable: 3 types of binary CGI-I ratings
    - "Minimally Improved" or better vs "No Change" or worse
    - "Much Improved" or better vs "Minimally Improved" or worse (most consistent with a clinically meaningful change)
    - "Very Much Improved" vs "Much Improved" or worse
- The clinically meaningful threshold was defined as the cutpoint for which specificity ≈ sensitivity

Results

Patients

- A total of 82 patients had corresponding percentage MCSF and CGI-I ratings for both caregivers and investigators and were included in this analysis
- The relationship between percentage reduction in seizure frequency and caregivers' and investigators' CGI-I ratings is shown in **Figure 1**

Figure 1. Change in MCSF From Baseline to End of Study by CGI-I Category (N=82)



Dark center line: the median percent change; lower and upper edges: 25th and 75th percentiles.

"Minimally Worse," "Much Worse," and "Very Much Worse" categories were pooled due to small n; the remaining CGI-I categories were plotted individually (ie, "No Change," "Minimally Improved," "Much Improved," and "Very Much Improved").

CGI-I, Clinical Global Impression of Improvement; MCSF, monthly convulsive seizure frequency.

ROC-Derived MCID Analyses

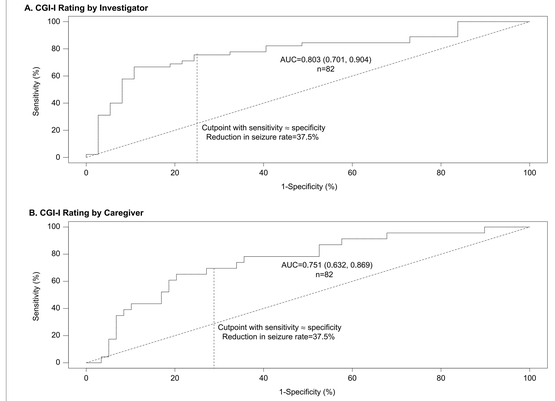
- A ≥37.5% reduction in MCSF was identified as the cutpoint for a "clinically meaningful change" for both caregiver and investigator CGI-I ratings (**Table 1**; **Figure 2**)
- The cutpoint for "Very Much Improved" required higher levels of reduction in MCSF for the caregiver rating (40% and 50% for investigator and caregiver ratings, respectively)

Table 1. ROC Analysis

CGI-I Category	Change in MCSF Cutpoint (%)	Sensitivity (%)	Specificity (%)	Correct (%)
Caregiver Assessment of CGI-I				
Very Much Improved	-50	67	74	73
Much Improved or better (clinically meaningful)	**-37.5**	**70**	**71**	**71**
Minimally Improved or better	-19.5	79	78	78
Investigator Assessment of CGI-I				
Very Much Improved	-40	64	63	63
Much Improved or better (clinically meaningful)	**-37.5**	**77**	**75**	**76**
Minimally Improved or better	-20	76	76	76

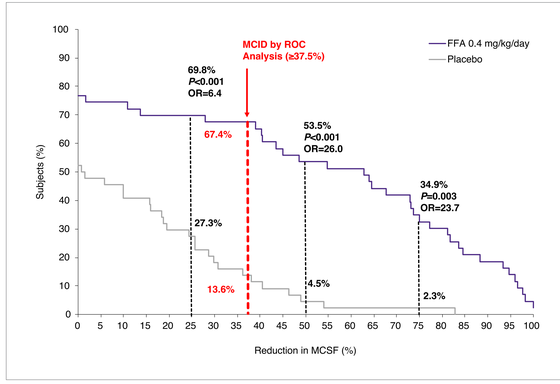
CGI-I, Clinical Global Impression of Improvement; MCSF, monthly convulsive seizure frequency; ROC, receiver operator characteristic.

Figure 2. ROC Curve: Percent Change in MCSF Relative to (A) Investigator or (B) Caregiver CGI-I Ratings of ≤2 ("Much Improved" or Better) vs >2 ("Minimally Improved" or Worse) After 14 Weeks of FFA Treatment



AUC, area under the curve; CGI-I, Clinical Global Impression of Improvement; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; ROC, receiver operator characteristic.

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



[a]P<0.001; *P* values are vs placebo. FFA, fenfluramine; MCID, minimal clinically important difference; MCSF, monthly convulsive seizure frequency; OR, odds ratio vs placebo; ROC, receiver operator characteristic.

Conclusions

- A threshold of ≥37.5% reduction in seizure frequency was best 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
  - Is slightly lower than the ≥44% reduction reported in a study of patients administered FFA with STP-free AED regimens (Study 1)[5]
    - May reflect the critical need and expectations of families of patients receiving STP-inclusive AED regimens as compared with those not on an 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 caregiver and investigator CGI-I ratings (eg, non-seizure outcomes on disease comorbidities and drug tolerability)

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