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ZX008 (Fenfluramine Hydrochloride Oral Solution) in Dravet Syndrome: Comparison of Study 1 Results Using 4-Week Versus 6-Week Baseline Seizure Collection

ZOGENIX

Joseph Sullivan[1]; Glenn Morrison[2]; Michael Lock[2]; Gail M. Farfel[2]

[1]University of California San Francisco, Benioff Children's Hospital, San Francisco, CA, USA; [2]Zogenix, Inc., Emeryville, CA, USA

Introduction

- Two phase 3 clinical studies of add-on fenfluramine (FFA) in patients with Dravet syndrome (DS) showed statistically significant reduction from baseline in monthly convulsive seizure frequency (MCSF)[1,2]
- Given the variability in seizure presentation in DS, FFA Studies 1 and 1504 were designed with a 6-week baseline period[3]
  - Establishing a stable baseline seizure frequency may be complicated by poor seizure control in patients with high seizure burden and spontaneous fluctuations in seizure frequency[4]
- In 2018, stiripentol and cannabidiol were approved in the US for the treatment of DS
  - Both studies used a 4-week baseline period[5,6]
  - A shorter baseline period may increase variability in measurements of the baseline MCSF and, consequently, result in higher variability in assessments of change from baseline
- In the present analysis, we evaluated the impact of a 4-week instead of a 6-week baseline period on clinical outcomes in one of the FFA phase 3 studies

Objective

- To assess the impact of shortening the baseline period (from the protocol-specified 6 weeks to 4 weeks) on comparisons of FFA to placebo in change from baseline in MCSF

Methods

Patients

- Key inclusion criteria
  - Children and young adults (ages 2 to 18 years, inclusive) with a diagnosis of DS
  - Seizures were not completely controlled by current AED regimen
  - Stable AED regimen (≥4 weeks prior to enrollment; could include ketogenic diet and/or vagus nerve stimulation)
  - Inclusion and randomization criteria for baseline convulsive seizure frequency for the original study design and for the re-analysis are presented in **Table 1**
    - Re-analysis assessed MCSF in the 28 days immediately preceding the day of randomization
- Key exclusion criteria
  - Concomitant treatment with stiripentol, cannabinoid products, or modulators of serotonergic activity
  - Clinically significant condition other than epilepsy, clinically relevant symptoms, or clinically significant illness in the 4 weeks prior to the Screening Visit that would negatively impact study participation or data collection or pose risk to the patient
  - Pulmonary hypertension or current/past history of cardiovascular or cerebrovascular disease (eg, cardiac valve regurgitation, myocardial infarction, or stroke)

Table 1. Baseline Convulsive[a] Seizure Frequency Criteria in Original Analysis and Re-Analysis

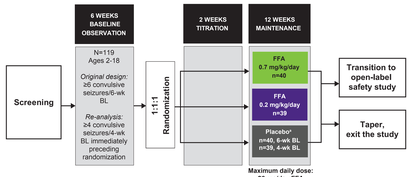
Criterion	Original Analysis	Re-Analysis
Length of baseline (weeks)	6	4
No. of CS during entire baseline period	≥6	≥4
No. of CS during first and second halves of baseline period	≥2 seizures in Weeks 1-3, and ≥2 seizures in Weeks 4-6	≥1 seizure in Weeks 1-2, and ≥1 seizure in Weeks 3-4

[a]Convulsive seizures were defined as hemiclonic, tonic-clonic, tonic, clonic, generalized tonic-clonic, or focal with clear observable motor signs.
CS, convulsive seizures.

Study Design

- Data were from Study 1, a phase 3 randomized placebo-controlled clinical study in patients with DS (NCT02682927; NCT02826863)
- Patients were randomized in a 1:1:1 ratio to twice-daily add-on FFA (0.7 or 0.2 mg/kg/day; maximum, 26 mg/day) or placebo (**Figure 1**)
  - FFA was administered as ZX008, an oral solution of FFA HCl containing 2.2 mg/mL FFA

Figure 1. Study Design



[a]In the baseline re-analysis, 1 patient in the placebo group who met the 6-week baseline criteria did not meet the 4-week baseline criteria and was excluded from the analysis.
BL, baseline; FFA, fenfluramine.

Efficacy Endpoints

- Endpoints were evaluated using either a 6-week or 4-week baseline period; in either case, the baseline period immediately preceded the day of the first study treatment (**Table 1**)
- Primary efficacy endpoint
  - Estimated percentage difference from placebo in MCSF after 0.7 mg/kg/day FFA, from baseline compared to the combined 14-week titration and maintenance (T+M) period
- Key secondary endpoints comparing 4- vs 6-week baseline
  - Median change in the percentage reduction in MCSF vs placebo after FFA, from baseline to the combined T+M period
  - Proportion of patients with ≥25%, ≥50%, or ≥75% reduction from baseline in MCSF
  - Subgroup analyses: baseline seizure burden, patient age

Statistical Analyses

- Difference from placebo in MCSF was analyzed using analysis of covariance (ANCOVA)
  - Factors and covariate: Treatment (3 levels) and age group (<6 years, ≥6 years), log baseline MCSF
  - Response: Log MCSF in the T+M periods
- Treatment groups were compared on median change in percentage MCSF using a Wilcoxon rank-sum test
- Responder analyses and treatment group comparisons were evaluated statistically by logistic regression using age group as a factor and log baseline MCSF as a covariate
- $P<0.05$ (two-sided) was the threshold for statistical significance

Results

Patients

- A total of 119 patients with DS were randomized to treatment (n=40, 0.7 mg/kg/day; n=39, 0.2 mg/kg/day; n=40, placebo) in the original analysis of Study 1
- Baseline characteristics are shown in **Table 2**

Baseline MCSF

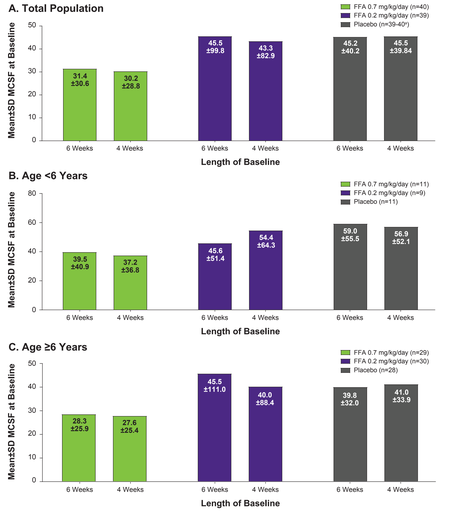
- Baseline seizure frequency at 4 weeks was comparable to 6 weeks within each treatment group (**Figure 2**)
  - In the baseline re-analysis, 1 patient in the placebo group who met the 6-week baseline criteria did not meet the 4-week baseline criteria and was excluded from the re-analysis (n=39 vs n=40)

Table 1. Patient Baseline Characteristics

	FFA 0.7 mg/kg/day	FFA 0.2 mg/kg/day	Placebo
n	40	39	40
Age (years), mean±SD (min, max)	8.8±4 (2, 18)	9.0±4.5 (2, 17)	9.2±5.1 (2, 18)
Age group <6 years, n (%)	11 (28)	9 (23)	11 (28)
Male, n (%)	21 (52)	22 (56)	21 (52)
Race, n (%)			
Caucasian	34 (85)	33 (85)	31 (78)
Asian	1 (3)	2 (5)	4 (10)
Other or not reported[a]	5 (12)	4 (10)	5 (12)
BMI (kg/m^2), mean±SD	18.5±3.5	19.3±5.7	18.0±3.8

[a]Not reported or missing; privacy laws in some regions/countries preclude disclosure of certain personal information.
BMI, body mass index; FFA, fenfluramine; SD, standard deviation.

Figure 2. Baseline Mean MCSF (6-Week vs 4-Week Baseline)

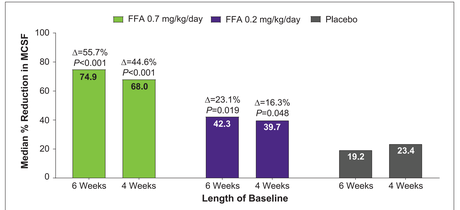


[a]In the baseline re-analysis, 1 patient in the placebo group who met the 6-week baseline criteria did not meet the 4-week baseline criteria and was excluded from the analysis.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; SD, standard deviation.

Efficacy Endpoints: Comparing 6-Week vs 4-Week Baseline

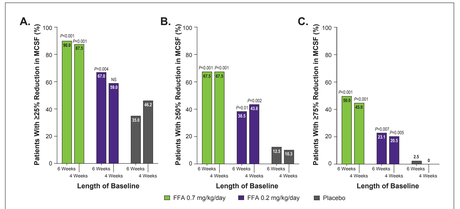
- MCSF reduction after FFA compared to placebo was comparable whether a 6- or 4-week baseline was used (**Figures 3 and 4**)
- Confidence intervals were slightly wider for the primary efficacy endpoint analyzed by 6- vs 4-week baseline, but MCSF reduction after FFA compared to placebo in the T+M periods was nearly identical in the 2 analyses (**Figure 5**)

Figure 3. Median Percentage Reduction in MCSF From Baseline vs Combined T+M Periods



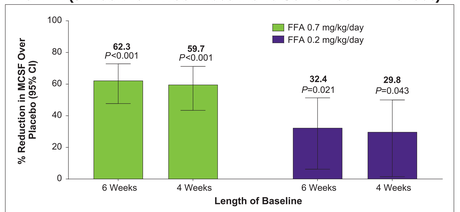
P-values are vs placebo; Δ, active minus placebo.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods.

Figure 4. Proportion of Patients with (A) ≥25%, (B) ≥50%, or (C) ≥75% Reduction in MCSF Baseline vs Combined T+M Periods



P-values are vs placebo.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods.

Figure 5. Primary Efficacy Analysis: MCSF Difference From Placebo After FFA (6-Week vs 4-Week Baseline vs Combined T+M Periods)

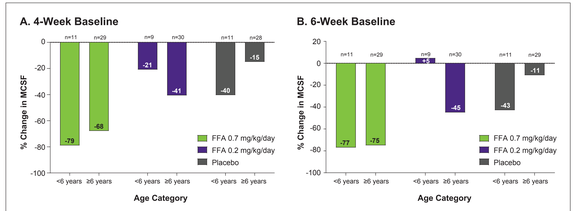


P-values are vs placebo.
CI, confidence interval; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency, T+M, combined titration and maintenance periods.

Efficacy Endpoints: Patient Subgroups Using a 4-Week Baseline

- Using a 4-week compared to a 6-week baseline, MCSF reduction by FFA 0.2 mg/kg/day was more pronounced in patients <6 years of age (**Figure 6**)

Figure 6. Percent Reduction From Baseline to T+M in Median MCSF After FFA by Age



FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods.

Conclusions

- Re-analysis of the results assuming a 4- vs 6-week baseline period:
  - Produced small changes in baseline seizure frequency
  - Slightly wider confidence intervals in the primary endpoint
  - Did not affect the conclusions or the statistical significance of convulsive seizure clinical outcomes in the primary and most secondary outcomes
    - The re-analysis by age group (<6 or ≥6 years), in which the younger group had a small n, was affected by the shorter baseline in the 0.2 mg/kg/day FFA group
- In Study 1, patients treated with FFA experienced statistically significant, clinically meaningful reductions in MCSF compared with patients treated with placebo
- The majority of patients were responders with ≥50% reduction in MCSF
- Future treatment studies in DS and other developmental and epileptic encephalopathies could use a 4-week baseline period to reduce overall burden on patients and families

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