3.431

ZX008 (Fenfluramine Hydrochloride Oral Solution) Reduces Seizure Burden by Significantly Increasing Number of Seizure-Free Days and Time Between Seizures in Patients With Dravet Syndrome

ZOGENIX

Joseph Sullivan[1]; Orrin Devinsky[2]; Bradley S. Galer[3]; Gail M. Farfel[3]; Douglas Haney[4]; M. Scott Perry[5]; Stephane Auvin[6]; Antonio Gil-Nagel[7]; Arnold R. Gammaitoni[3]

[1]University of California San Francisco, Benioff Children's Hospital, San Francisco, CA, USA; [2]NYU Langone Medical Center, New York, NY, USA; [3]Zogenix, Inc., Emeryville, CA, USA; [4]Independent Statistical Consultant, Burlingame, CA, USA; [5]Cook Children's Medical Center, Fort Worth, TX, USA; [6]Robert Debré Children's Hospital, Paris, France; [7]Hospital Ruber Internacional, Madrid, Spain

Introduction

- Dravet syndrome (DS) is a rare, early-onset, treatment-resistant epileptic encephalopathy that negatively affects the health-related quality of life (QoL) of patients, caregivers, and families[1-4]
- Caregivers cite the unpredictability and severity of seizure events as key concerns leading to high levels of anxiety and stress in caring for patients with DS[2,5]
  - Reduction in seizure frequency alone does not adequately convey whether patients with residual seizures have moved meaningfully toward seizure freedom, especially in patients with high baseline seizure burden
- Here, an alternative analysis of the data from Study 1, a phase 3, double-blind, parallel-group, placebo-controlled study (NCT02682927/NCT02826863), is presented focusing on seizure-free intervals and the number of seizure-free days, using a time-to-event (TTE) analysis approach

Methods

- 119 patients with DS (ages 2-18, inclusive) who were enrolled in Study 1 were included in this analysis
- Patients were followed for a 6-week baseline period and then randomized 1:1:1 to receive treatment with fenfluramine (FFA) 0.7 mg/kg/day (maximum of 26 mg/day), FFA 0.2 mg/kg/day, or placebo added to their current antiepileptic drug regimen
  - Doses were titrated during the first 2 weeks and then maintained for an additional 12 weeks
  - FFA was administered as FFA HCl oral solution containing 2.2 mg/mL FFA
- Endpoints:
  - Protocol-specified secondary endpoints: number of convulsive seizure-free days and longest interval between convulsive seizures
  - Post-hoc analysis endpoint: TTE analysis, with time to event defined as the time required during the treatment period to experience the same number of seizures (ie, "Nth" seizure) that had occurred during the baseline period

Statistical Analysis

- Differences among each FFA treatment group versus placebo for the number of convulsive seizure-free days were evaluated using an analysis of covariance (ANCOVA) model (α=0.05)
- Differences among each FFA treatment group versus placebo for the longest interval between convulsive seizures were evaluated using the Wilcoxon rank sum test
- Differences between Kaplan-Meier TTE curves for each FFA treatment vs placebo were assessed using the log-rank test
- Analyses were performed with the intent-to-treat population
  - Data were censored for patients who did not reach baseline seizure frequency by Week 14 or time of study discontinuation, or had a substantial number (>10%) of missing diary days

Results

Patients

- Demographics and baseline characteristics are presented in **Table 1**

Table 1. Patient Demographics and Baseline Characteristics

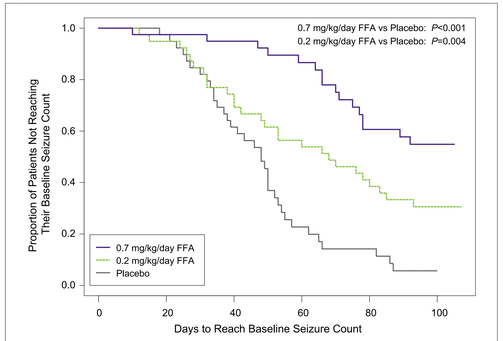
	FFA 0.7 mg/kg/day	FFA 0.2 mg/kg/day	Placebo
n	40	39	40
Age, years			
Mean±SD (median)	8.8±4.4 (8.5)	9.0±4.5 (8.0)	9.2±5.1 (8.5)
Min, max	2, 18	2, 17	2, 18
Age group <6 years, n (%)	11 (28)	9 (23)	11 (28)
Males, n (%)	21 (52)	22 (56)	21 (52)
Race, n (%)			
Caucasian	34 (85)	33 (85)	31 (78)
Asian	1 (3)	2 (5)	4 (10)
Other or not reported[a]	5 (12)	4 (10)	5 (12)
Median (min, max) number of seizures during 6-week baseline period	26.0 (7, 186)	25.0 (7, 913)	40.5 (5, 221)
Baseline seizure-free days per 28 days			
Mean±SD (median)	15.2±7.6 (17.6)	16.4±6.7 (18.7)	13.3±7.7 (13.3)
Min, max	0.0, 24.0	0.0, 24.7	0.0, 24.7

FFA, fenfluramine; SD, standard deviation.
[a]Privacy laws in some regions preclude disclosure of certain personal information.

Efficacy

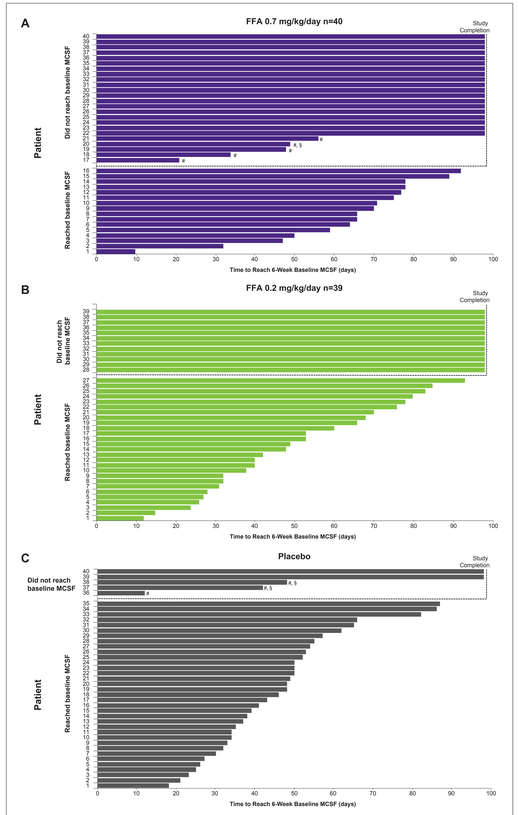
- Patients in the FFA 0.7 mg/kg/day dose group took significantly longer to reach baseline seizure count than patients receiving placebo (**Figures 1 and 2**)
  - Median TTE was ~7 weeks for placebo, ~10 weeks for FFA 0.2 mg/kg/day, and >12 weeks for FFA 0.7 mg/kg/day (*P*<0.001)
  - In the FFA 0.7 mg/kg/day group, ~60% of patients never reached baseline seizure count and were censored

Figure 1. Time to Reach Baseline Seizure Count



FFA, fenfluramine.

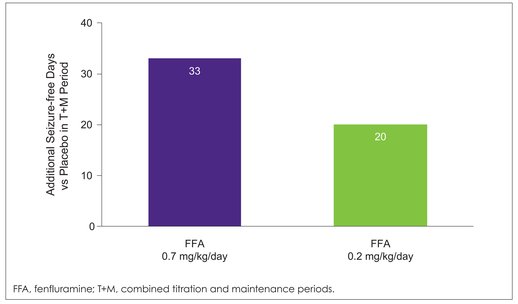
Figure 2. Individual Patient Time to Reach Baseline Seizure Count by Treatment Group (A) Fenfluramine 0.7 mg/kg/day, (B) Fenfluramine 0.2 mg/kg/day, and (C) Placebo



#Patient did not complete the trial.
§Data censored due to substantial number (>10%) of missing diary days.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency.

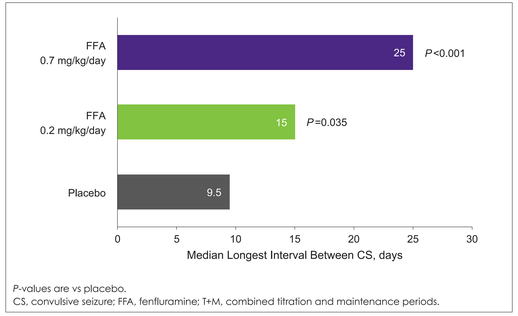
- FFA (0.7 mg/kg/day) provided significantly more convulsive seizure-free days (**Figure 3**) and longer intervals of seizure freedom (**Figure 4**) compared to placebo
  - During treatment, median numbers of seizure-free days per 28 days were 24, 21, and 15 days in the FFA 0.7 mg/kg/day, FFA 0.2 mg/kg/day, and placebo groups, respectively
  - Seizure freedom was experienced by 3 (8%) patients each in the FFA 0.7 mg/kg/day and 0.2 mg/kg/day groups and in 0 patients in the placebo group
  - Only one seizure was reported in 7 (18%) patients in the 0.7 mg/kg/day group, 2 (5%) patients in the 0.2 mg/kg/day group, and 0 patients in the placebo group

Figure 3. Additional Number of Seizure-Free Days per 14 Weeks vs Placebo



FFA, fenfluramine; T+M, combined titration and maintenance periods.

Figure 5. Median Longest Interval Between Convulsive Seizures in the T+M Period



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

Safety

- The most common adverse events (≥10% of patients) occurring more frequently with FFA were decreased appetite, diarrhea, fatigue, lethargy, pyrexia, somnolence, and decreased weight (**Table 2**)
- No valvular heart disease or pulmonary arterial hypertension was observed in any patient at any time

Table 2. Non-Cardiovascular Adverse Events Occurring in ≥10% of Patients in Any Treatment Group

	FFA 0.7 mg/kg/day (n=40)	FFA 0.2 mg/kg/day (n=39)	Placebo (n=40)
Patients with ≥1 adverse event, n (%)	38 (95)	37 (95)	26 (65)
Decreased appetite	15 (38)	8 (20)	2 (5)
Diarrhea	7 (18)	12 (31)	3 (8)
Fall	0 (0.0)	4 (10)	2 (5)
Fatigue	4 (10)	4 (10)	1 (2)
Lethargy	7 (18)	4 (10)	2 (5)
Nasopharyngitis	7 (18)	4 (10)	5 (12)
Pyrexia	2 (5)	7 (18)	8 (20)
Seizure	3 (8)	4 (10)	5 (12)
Somnolence	4 (10)	6 (15)	3 (8)
Upper respiratory tract infection	0 (0.0)	8 (21)	5 (12)
Vomiting	3 (8)	4 (10)	4 (10)
Weight decreased	2 (5)	5 (13)	0 (0.0)

FFA, fenfluramine.

Conclusions

- FFA extended the TTE and provided significantly more seizure-free days and longer intervals of seizure freedom than placebo
- TTE analysis demonstrated statistical significance for both treatment groups compared to placebo (*P*<0.001 for 0.7 mg/kg/day FFA; *P*=0.004 for 0.2 mg/kg/day FFA), with ~60% of patients in the 0.7 mg/kg/day group never reaching baseline seizure count
- These results demonstrate the ability of FFA to significantly reduce day to day seizure burden in patients with DS, which may in turn help reduce the physical and emotional toll of the disease and improve health-related QoL for both the patient and caregiver
- FFA was generally well tolerated
- There was no evidence of cardiotoxicity, with no cases of valvular heart disease or pulmonary arterial hypertension

References

1. Dravet C. *Epilepsia.* 2011;52(suppl 2):3-9.
2. Jensen MP, et al. *Epilepsy Behav.* 2017;74:135-43.
3. Scheffer IE, et al. *Epilepsia.* 2017;58(4):512-21.
4. Gataullina S, Dulac O. *Seizure.* 2017;44:58-64.
5. Kroner BL, et al. *J Pediatr Health Care.* 2018;32(4):348-55.

Acknowledgments

The studies described in this poster were sponsored by Zogenix, Inc. (Emeryville, CA, USA). Professional medical writing and editing were provided to the authors by Diana Secora, PhD, and Barbara Schwedel, MS, ELS, of PharmaWrite (Princeton, NJ, USA) and were paid for by Zogenix.

Disclosures

JS: Research grants, travel support, Zogenix; Consultant/Advisor, Dravet Syndrome Foundation, Epygenix; Reviewer, Epilepsy Study Consortium; **OD:** Received research grants from Zogenix during the conduct of the study, and received research grants from Novartis and PTC Therapeutics and has equity interest in Rettco, Pairnomix, Tilray, and Egg Rock Holdings outside the submitted work; **BSG, GMF, and ARG:** Employment, Ownership interest in Zogenix, Inc.; **DH:** Consultant, Zogenix; **MSP:** Research support, Zogenix and Greenwich Biosciences; honoria for speakers' bureau and advisory/consulting for Stoke Therapeutics, Encoded Therapeutics, and Biocodex; **SA:** Reports personal fees from Arvelle and Biocodex; personal fees and nonfinancial support from Biomarin, GW Pharma, and Nutricia; personal fees and grants from Eisai, UCB Pharma, and Advicenne Pharma for work as an investigator; and nonfinancial support from Vitaflo; **AGN:** Reports personal fees from Bilal, GW Pharma, Zogenix, Stoke Therapeutics, Eisai, and Esteve.

Presented at the American Epilepsy Society (AES) Annual Meeting, December 6–10, 2019, Baltimore, MD, USA