Fenfluramine HCl Significantly Reduces Frequency of Generalized Tonic-Clonic Seizures in Dravet Syndrome: Pooled Analysis From Two Phase 3 Clinical Trials

ZOGENIX

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Introduction

- Dravet syndrome is a severe, treatment-refractory developmental epileptic encephalopathy in which generalized tonic-clonic seizures are a common seizure type often refractory to treatment
- Patients with Dravet syndrome experience elevated disease-specific mortality, most commonly due to sudden unexpected death in epilepsy (SUDEP) or status epilepticus[1]
  - Dravet SUDEP rate is ~9.3 per 1000 person-years of observation[1]
  - >6 times higher than in the general population of people with epilepsy[2]
- Generalized tonic-clonic seizures are a major risk factor for SUDEP[3]
- This post-hoc analysis explored the impact of fenfluramine on generalized tonic-clonic seizures and focal-to-bilateral tonic-clonic seizures in patients enrolled in two Phase 3 clinical trials of fenfluramine added to current antiepileptic drug regimens

Methods

- Patients with Dravet syndrome aged 2-18 years enrolled in 1 of 2 randomized, placebo-controlled clinical trials of fenfluramine
- Eligible patients were randomized to placebo or fenfluramine at 0.2 or 0.7 mg/kg/day (maximum daily dose of 26 mg/day) in patients not currently receiving stiripentol, or fenfluramine at 0.4 mg/kg/day (maximum daily dose of 17 mg/day) in patients also treated with stiripentol
- Fenfluramine was administered as an oral solution of fenfluramine HCl containing 2.2 mg/mL fenfluramine
- An electronic diary was used to capture seizure frequency

Results

- 206 patients were enrolled and randomized to placebo (n=84) or fenfluramine 0.2 mg/kg/day (n=39), 0.4 mg/kg/day (n=43), or 0.7 mg/kg/day (n=40)
- Baseline patient characteristics are shown in **Table 1**

Table 1. Demographic and Baseline Characteristics

	Placebo	FFA 0.2 mg/kg/day	FFA 0.4 mg/kg/day + STP	FFA 0.7 mg/kg/day
N	84	39	43	40
Age (years), mean±SD (median)	9.3±5.0 (9.0)	9.0±4.5 (8.0)	8.8±4.6 (9.0)	8.8±4.4 (8.5)
Age group, n (%)				
≥6 years	61 (72.6)	30 (76.9)	31 (72.1)	29 (72.5)
Sex, n (%)				
Male	48 (57.1)	22 (56.4)	23 (53.5)	21 (52.5)
Female	36 (42.9)	17 (43.6)	20 (46.5)	19 (47.5)
Race, n (%)				
White	60 (71.4)	33 (84.6)	23 (53.5)	34 (85.0)
Black or African-American	2 (2.4)	0	1 (2.3)	0
Asian	5 (6.0)	2 (5.1)	2 (4.7)	1 (2.5)
American Indian or Alaska Native	1 (1.2)	1 (2.6)	0	0
Other	1 (1.2)	0	3 (7.0)	0
Not reported[a]	15 (17.9)	3 (7.7)	14 (32.6)	5 (12.5)
Generalized tonic-clonic seizure frequency per 28 days				
N[b]	71	29	39	31
Mean±SD	20.1±24.2	26.2±33.8	23.1±37.3	15.5±19.0
Median (min, max)	10.7 (1.3, 127.3)	12.3 (2.7, 140.0)	8.0 (2.0, 211.3)	8.7 (0.7, 78.0)
Focal-to-bilateral tonic-clonic seizure frequency per 28 days				
N[b]	21	6	3	11
Mean±SD	11.2±13.4	6.3±5.6	1.8±1.0	5.4±4.6
Median (min, max)	4.7 (0.7, 49.2)	4.7 (0.7, 14.0)	2.0 (0.7, 2.7)	4.7 (0.7, 14.7)

Fenfluramine doses are expressed as base-equivalent mg/kg/day.
[a]Due to privacy laws in Europe many patients did not report race.
[b]Number of patients demonstrating the seizure type.
FFA, fenfluramine; STP, stiripentol.

Figure 1. Effect of Fenfluramine on Frequency of Generalized Tonic-Clonic Seizures in Patients With Dravet Syndrome

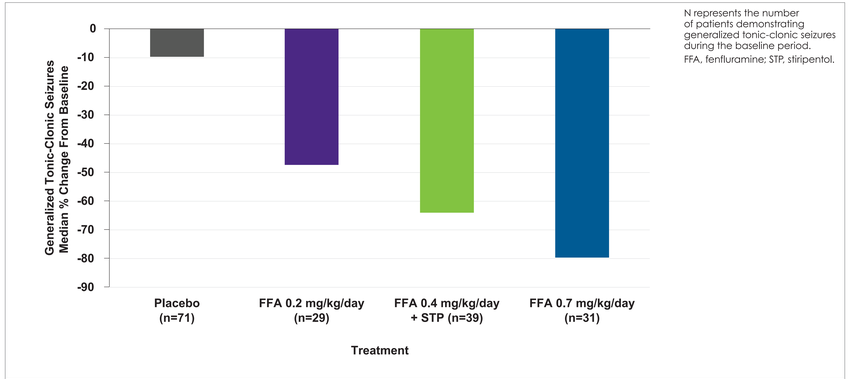
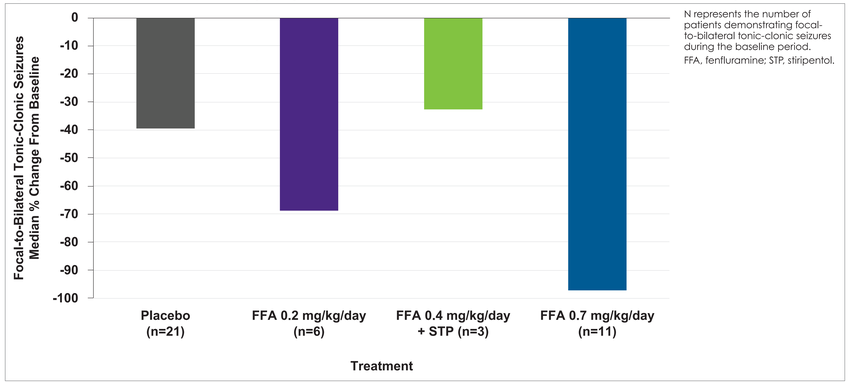


Figure 2. Effect of Fenfluramine on Frequency of Focal-to-Bilateral Tonic-Clonic Seizures in Patients With Dravet Syndrome



- Treatment-emergent adverse events are presented in **Table 2**
- No cases of cardiac valvular disease or pulmonary arterial hypertension occurred in any patient

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

	Placebo	FFA 0.2 mg/kg/day	FFA 0.4 mg/kg/day + STP	FFA 0.7 mg/kg/day	Any FFA dose
N	84	39	43	40	122
Decreased appetite	7 (8.3)	8 (20.5)	17 (39.5)	14 (35.0)	39 (32.0)
Lethargy	3 (3.6)	3 (7.7)	6 (14.0)	6 (15.0)	15 (12.3)
Fatigue	3 (3.6)	3 (7.7)	7 (16.3)	3 (7.5)	13 (10.7)
Somnolence	4 (4.8)	5 (12.8)	2 (4.7)	4 (10.0)	11 (9.0)
Diarrhoea	2 (2.4)	5 (12.8)	1 (2.3)	1 (2.5)	7 (5.7)

Values are given as n (%).
FFA, fenfluramine; STP, stiripentol.

Conclusions

- Fenfluramine provided clinically meaningful (≥50%) and profound (≥75%) reductions in the frequency of generalized tonic-clonic and focal-to-bilateral tonic-clonic seizures in patients with Dravet syndrome
- Fenfluramine may represent an important, effective new treatment option for patients with Dravet syndrome

References

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3. Harden C, et al. *Neurology*. 2017;88(17):1674-80.

Acknowledgments

This study was funded by Zogenix, Inc. (Emeryville, CA). Zogenix thanks all of the participants and the investigators involved in this study. Medical writing and editorial assistance were provided by Edward Weselcouch, PhD, and Don Fallon, ELS, of PharmaWrite, LLC (Princeton, NJ, USA), and were funded by Zogenix, Inc.

Disclosures

OD: Research funding, Zogenix (during the conduct of the study); Research funding, Novartis, PTC Therapeutics; Equity interest, Egg Rock Holdings, Pairnomix, Rettco, Tilray.

JHC: Research funding, Zogenix (during the conduct of the study); Research funding, GW Pharma; Consultant/advisor, Eisai, GW Pharma, Shire, Zogenix; Speaker, BioMarin, Shire, Zogenix.

AGN: Research funding, Eisai, UCB; Consultant, Eisai, European Dravet Foundation, GW Pharma, Zogenix.

BG: Research funding, GW Pharma, LivaNova, UCB, Zogenix; Consultant/advisor, GW Pharma, OVID/Takeda, Zogenix; Speaker, Eisai, LivaNova, UCB.

DB: Research funding, Zogenix.

KR: Research funding, Travel support, Consultant, Speaker; AFT Pharmaceuticals, Eisai Australia, Janssen-Cilag Pty, LivaNova Australia, Novartis, UCB, Zogenix International.

ARG, GMF, AM, BSG, GM: Employees, Zogenix; Ownership interest, Zogenix.

Presented as part of the Zogenix Scientific Exhibit during the American Epilepsy Society (AES) Annual Meeting, December 8, 2019, Baltimore, MD, USA