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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

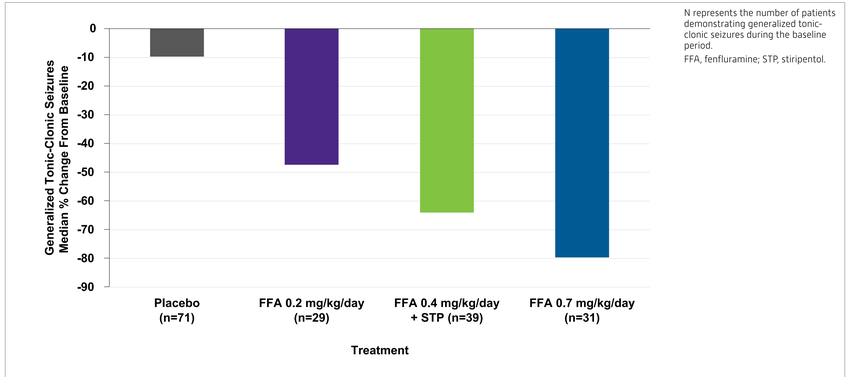
- 206 patients were enrolled and randomized to placebo (n=84) or fenfluramine 0.2 mg/kg/day (n=39), 0.4 mg/kg/day (n=43), or 0.7 mg/kg/day (n=40)
- Baseline patient characteristics are shown in **Table 1**

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)

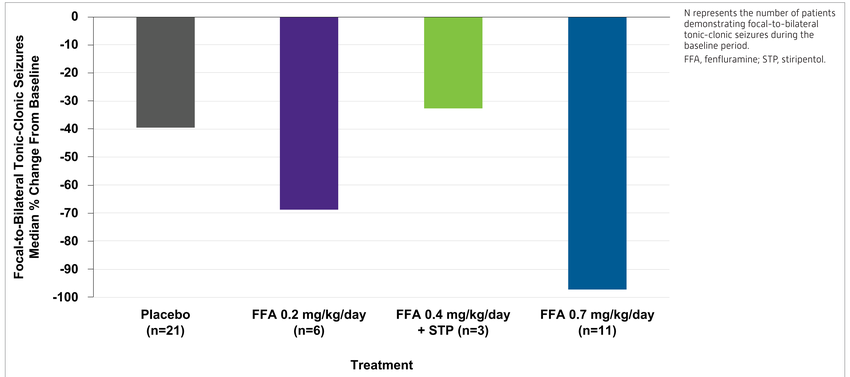
Fenfluramine doses are expressed as base-equivalent mg/kg/day.
[a]Due to privacy laws in Europe many patients did not report race.
[b]Number of patients demonstrating the seizure type.
FFA, fenfluramine; STP, stiripentol.

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



N represents the number of patients demonstrating generalized tonic-clonic seizures during the baseline period.
FFA, fenfluramine; STP, stiripentol.

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



N represents the number of patients demonstrating focal-to-bilateral tonic-clonic seizures during the baseline period.
FFA, fenfluramine; STP, stiripentol.

- 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

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