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ZX008 (Fenfluramine HCl Oral Solution) Provides Long-Term, Clinically Meaningful Reduction of Convulsive Seizure Frequency in Young (<6 Years Old) Dravet Syndrome Subjects: Analysis From a Long-Term Open-Label Study

ZOGENIX

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Introduction

- Dravet syndrome (DS) is a severe, drug-resistant epileptic encephalopathy that has its onset during the first year of life
- Current treatment options, commonly valproate, clobazam, and stiripentol, fully control tonic-clonic seizures in <25% of patients, and nearly 50% of treated patients continue to experience ≥4 tonic-clonic seizure per month[1]
- O'Reilly and colleagues recently reported[2] that uncontrolled seizures in early-onset epilepsy (<2 years of age) was significantly associated with poor cognitive outcomes, underscoring the need for earlier treatment options that can provide clinically meaningful, sustained reductions in seizure frequency
- Two recent Phase 3 clinical trials have reported dramatic decreases in the frequency of major motor seizures in children and adolescents with DS aged 2 to 18 years who were treated with oral fenfluramine added to their current antiepilepsy drug regimen[3,4]
- Here we present an analysis exploring the effectiveness of fenfluramine by age group in a long-term open-label extension study (OLE)

Methods

- Patients with DS aged 2 to 18 years who completed either of the two Phase 3 clinical trials entered an OLE of oral fenfluramine (NCT02823145)
  - All patients in the OLE study started treatment with a fenfluramine dose of 0.2 mg/kg/day, and the dose was titrated to optimal effect (maximum dose was 0.7 mg/kg/day; maximum total dose of 26 mg/day), or in patients who were also receiving stiripentol, to fenfluramine 0.4 mg/kg/day (maximum total dose of 17 mg/day)
  - Fenfluramine was administered as an oral solution of fenfluramine HCl containing 2.2 mg/mL fenfluramine
  - Baseline convulsive seizure frequency was determined during the baseline period in the core clinical trial
  - Effectiveness and tolerability were assessed at Months 1, 2, and 3, and thereafter at 3-month intervals

Results

- 158 patients who completed one of the two Phase 3 clinical trials enrolled in the OLE
  - Demographics and baseline characteristics are shown in **Table 1**
- 19/158 patients (12.0%) discontinued the OLE
  - Lack of efficacy (n=13)
  - Withdrawal by patients (n=2)
  - Physician decision (n=1)
  - Adverse event (n=1)
  - Sudden unexpected death in epilepsy (SUDEP) (n=1)
  - Other (n=1)
- 42/158 patients (26.6%) were <6 years old at entry into the core Phase 3 clinical trial

Table 1. Demographic and Baseline Characteristics

Characteristic	
N	158
Age (years), mean±SD (median)	9.2±4.8 (8.0)
Age group, n (%)	
<6 years	42 (26.6)
≥6 years	116 (73.4)
Sex, n (%)	
Male	90 (57.0)
Female	68 (43.0)
Race, n (%)	
White	121 (76.6)
Black or African-American	1 (0.6)
Asian	8 (5.1)
American Indian or Alaska Native	2 (1.3)
Other	2 (1.3)
Not reported[a]	24 (15.2)
Baseline weight (kg), mean±SD (median)	33.6±16.7 (28.7)
Baseline BMI (kg/m^2)	18.1±4.1 (17.3)

[a]Due to privacy laws in Europe many patients did not report race.
BMI, body mass index.

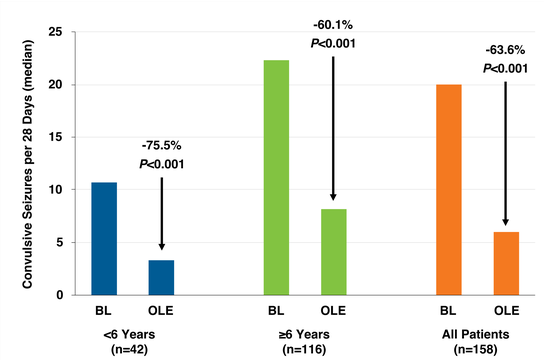
- Fenfluramine provided sustained, clinically meaningful reduction in convulsive seizure frequency in young patients (<6 years old) that was similar to that observed in older patients (≥6 years old) and in the entire patient population (**Table 2**, **Figure 1**)

Table 2. Convulsive Seizure Frequency per 28 Days

	Age Group		All Patients (N=158)
	<6 Years (n=42)	≥6 Years (n=116)	
Baseline MCSF			
Mean±SD	37.5±45.4	38.7±64.2	38.4±59.6
Median (min, max)	10.7 (4.0, 147.3)	22.3 (2.7, 623.5)	20.0 (2.7, 623.5)
Overall OLE treatment period			
Mean±SD	19.3±43.4	19.4±31.2	19.4±34.7
Median (min, max)	3.4 (0.0, 206.4)	8.2 (0.0, 188.9)	6.0 (0.0, 206.4)
Overall OLE treatment period % change from baseline			
Mean±SD	-52.0±66.1	-47.8±50.9	-48.9±55.2
Median (min, max)	-75.5 (-100, 227.3)	-60.1 (-100, 234.9)	-63.6 (-100, 234.9)
P-value	<0.001	<0.001	<0.001

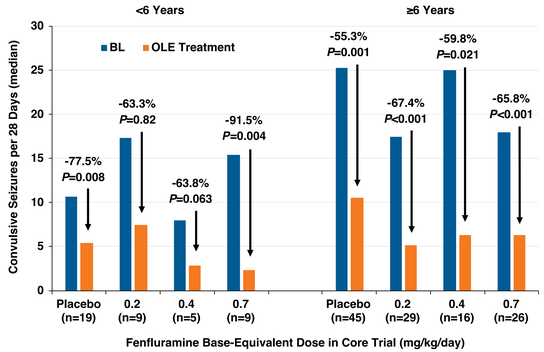
P-values are for median percent change from baseline and were estimated using the Wilcoxon signed-rank test.
MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

Figure 1. Long-Term Effectiveness of Fenfluramine on Convulsive Seizure Frequency by Age



The median percent change from baseline is shown for each subgroup.
P-values are for median percent change from baseline and were estimated using the Wilcoxon signed-rank test.
BL, baseline; OLE, open-label extension.

Figure 2. Long-Term Effectiveness of Fenfluramine on Convulsive Seizure Frequency by Age and Dose Group



Fenfluramine base-equivalent doses were used in the core clinical trials; in the OLE all patients started at 0.2 mg/kg/day and were individually titrated based on efficacy and tolerability.
P-values are for median percent change from baseline and were estimated using the Wilcoxon signed-rank test.
BL, baseline; OLE, open-label extension.

Safety

- No cases of valvular heart disease or pulmonary arterial hypertension were observed

Table 3. Most Common (≥10%) Non-Cardiovascular Treatment-Emergent Adverse Events (TEAEs) by Age Group

	<6 Years	≥6 Years
N	42	116
Diarrhoea	17 (40.5)	24 (20.7)
Vomiting	12 (28.6)	15 (12.9)
Fatigue	5 (11.9)	19 (16.4)
Pyrexia	24(57.1)	27 (23.3)
Ear infection	7 (16.7)	3 (2.6)
Gastroenteritis	8 (19.0)	2 (1.7)
Gastroenteritis viral	5 (11.9)	6 (5.2)
Influenza	6 (14.3)	14 (12.1)
Nasopharyngitis	14 (33.3)	28 (24.1)
Sinusitis	5 (11.9)	9 (7.8)
Upper respiratory tract infection	12 (28.6)	17 (14.7)
Pharyngitis	5 (11.9)	2 (1.7)
Viral infection	6 (14.3)	6 (5.2)
Fall	5 (11.9)	8 (6.9)
Decreased appetite	16 (38.1)	44 (37.9)
Cough	8 (19.0)	5 (4.3)
Constipation	1 (2.4)	12 (10.3)
Weight decreased	3 (7.1)	17 (14.7)
Lethargy	2 (4.8)	17 (14.7)
Seizure	10 (23.8)	25 (21.6)
Somnolence	8 (19.0)	12 (10.3)
Tremor	0	13 (11.2)

Values are given as n (%). Adverse events were classified as a TEAE if they started after the first dose of treatment in the core double-blind clinical trial. N refers to the number of patients reporting each TEAE.

Conclusions

- Treatment with fenfluramine provided sustained, clinically meaningful reduction in convulsive seizure frequency in young DS patients that was comparable to that observed in the older age group and overall patient population
- The robust response in the younger patient subgroup may be expected to mitigate longer-term negative neurodevelopmental outcomes[2]
- Fenfluramine was generally well tolerated and no case of valvular heart disease or pulmonary arterial hypertension was observed in any patient at any time

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