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# ZX008 (Fenfluramine Hydrochloride Oral Solution) Provides Clinically Meaningful Reductions in Seizure Frequency Irrespective of Concomitant AEDs Commonly Used in Dravet Syndrome: Pooled Analysis of Two Phase 3 Trials

ZOGENIX


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## Introduction

- Dravet syndrome (DS) is a rare and severe form of epilepsy characterized by medically intractable seizures[1]
- As drug resistance is a hallmark of DS, patients often require polypharmacy with multiple concomitant antiepileptic drugs (AEDs) for seizure management[2,3]
- The objective of this analysis was to evaluate the efficacy of adjunctive fenfluramine (FFA, administered as ZX008, an oral solution of FFA HCl containing 2.2 mg/mL FFA) when used in combination with any of the various AEDs that are commonly used in DS, including stiripentol, clobazam, valproate, and/or the combination of clobazam/valproate

## Methods

- Patients with Dravet syndrome (aged 2-19 years, inclusive) who were enrolled in one of two double-blind, parallel-group, placebo-controlled phase 3 studies (Study 1, NCT02682927, NCT02826863; Study 1504, NCT02926898) were included in this analysis
  - Depending on the study, patients received FFA doses ranging from 0.2 to 0.7 mg/kg/day (maximum daily doses: 26 mg/day without stiripentol [Study 1] and 17 mg/day with stiripentol [Study 1504])
  - Study 1 had a 2-week titration (total treatment period 14 weeks), while Study 1504 had a 3-week titration (total treatment period 15 weeks)
- Percent difference in convulsive seizure frequency per 28 days (monthly convulsive seizure frequency, MCSF) was calculated from baseline relative to the combined titration and maintenance periods
- Differences among subgroups were statistically evaluated using an analysis of covariance (ANCOVA) model ($\alpha$=0.05)

## Results

### Patients

- A total of 206 patients with DS were enrolled in the double-blind studies (placebo: n=84; 0.2 mg/kg/day FFA: n=39; 0.4 mg/kg/day FFA: n=43; 0.7 mg/kg/day FFA: n=40)
- Demographics are presented in **Table 1**

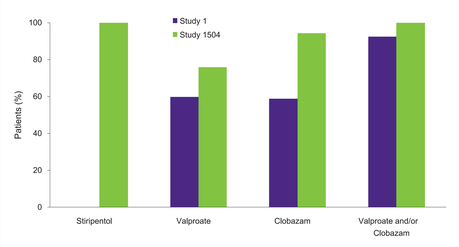
**Table 1. Patient Demographics and Baseline Characteristics**

| | Overall |
|---|---|
| N | 206 |
| Age (years), mean±SD (median) | 9.0±4.7 (8.5) |
| Min, max | 2, 19 |
| Age group ≥6 years, n (%) | 151 (73.3) |
| Male, n (%) | 114 (55.3) |
| Race, n (%) | |
| Caucasian | 150 (72.8) |
| Not reported[a] | 37 (18.0) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 21 (10.2) |
| Not Hispanic or Latino | 140 (68.0) |
| Not reported[a] | 39 (18.9) |
| Unknown[a] | 6 (2.9) |
| Region | |
| Canada or US | 101 (49.0) |
| Europe/Australia | 105 (51.0) |
| BMI (kg/m$^2$), mean±SD (median) | 18.4±4.3 (17.4) |
| Min, max | 11.6, 42.8 |

BMI, body mass index; SD, standard deviation.
[a]Privacy laws in some regions/countries preclude disclosure of certain personal information.

- The most commonly used AEDs were stiripentol (Study 1504 only), valproate, and clobazam (**Figure 1**)

**Figure 1. Most Common Concomitant Antiepileptic Treatments in the Safety Population per Study[a]**

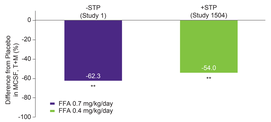



[a]Use of stiripentol was an exclusion criterion for Study 1; formulations of both salts and acids were used for valproate, including valproate sodium, valproate semisodium, and valproate.

### Efficacy

- FFA provided a significant benefit in patients when used as adjunctive therapy in combination with common AED regimens (**Figures 2-5**)

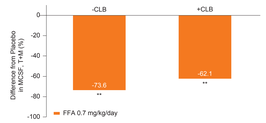
**Figure 2. Change in Monthly Convulsive Seizure Frequency With and Without Stiripentol**




| | Study 1 Seizure Frequency per 28 days | | Study 1504 Seizure Frequency per 28 days | |
|---|---|---|---|---|
| | FFA 0.7 mg/kg/day (n=40) | Placebo (n=40) | FFA 0.4 mg/kg/day (n=43) | Placebo (n=44) |
| Baseline: | | | | |
| Median | **21.2** | **31.4** | **14.0** | **10.7** |
| Min, max | 4.9, 127.0 | 3.3, 147.3 | 2.7, 213.3 | 2.7, 162.7 |
| T+M period: | | | | |
| Median | **5.4** | **26.0** | **5.2** | **11.4** |
| Min, max | 0.0, 169.9 | 3.2, 180.6 | 0.0, 458.6 | 2.2, 170.1 |

**$P$<0.001, difference from placebo.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; STP, stiripentol; T+M, combined titration and maintenance periods.

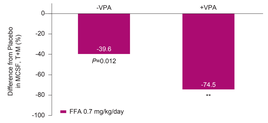
**Figure 3. Change in Monthly Convulsive Seizure Frequency With and Without Clobazam**




| | Seizure Frequency per 28 days + CLB | | Seizure Frequency per 28 days - CLB | |
|---|---|---|---|---|
| | FFA 0.7 mg/kg/day (n=25) | Placebo (n=64) | FFA 0.7 mg/kg/day (n=15) | Placebo (n=20) |
| Baseline: | | | | |
| Median | **11.3** | **18.0** | **25.7** | **21.3** |
| Min, max | 4.8, 124 | 2.7, 162.7 | 4.8, 100.0 | 3.3, 113.3 |
| T+M period: | | | | |
| Median | **4.9** | **15.9** | **4.6** | **12.5** |
| Min, max | 0.0, 169.9 | 2.2, 170.1 | 0.0, 54.9 | 3.0, 133.1 |

**$P$<0.001, difference from placebo.
CLB, clobazam; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods.

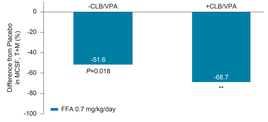
**Figure 4. Change in Monthly Convulsive Seizure Frequency With and Without Valproate**




| | Seizure Frequency per 28 days + VPA | | Seizure Frequency per 28 days – VPA | |
|---|---|---|---|---|
| | FFA 0.7 mg/kg/day (n=27) | Placebo (n=67) | FFA 0.7 mg/kg/day (n=13) | Placebo (n=17) |
| Baseline: | | | | |
| Median | **14.7** | **14.0** | **46.7** | **34.0** |
| Min, max | 4.8, 100 | 2.7, 162.7 | 4.8, 124.0 | 6.7, 134.7 |
| T+M period: | | | | |
| Median | **1.7** | **11.6** | **24.2** | **31.2** |
| Min, max | 0.0, 169.9 | 2.2, 170.1 | 0.3, 61.0 | 3.0, 164.0 |

**$P$<0.001, difference from placebo.
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods; VPA, valproate.

**Figure 5. Change in Monthly Convulsive Seizure Frequency With and Without the Combination of Clobazam/Valproate**




| | Seizure Frequency per 28 days + VPA/CLB | | Seizure Frequency per 28 days – VPA/CLB | |
|---|---|---|---|---|
| | FFA 0.7 mg/kg/day (n=36) | Placebo (n=78) | FFA 0.7 mg/kg/day (n=4) | Placebo (n=6) |
| Baseline: | | | | |
| Median | **15.1** | **19.7** | **77.0** | **20.0** |
| Min, max | 4.8, 124 | 2.7, 162.7 | 54.7, 84.7 | 6.7, 74.0 |
| T+M period: | | | | |
| Median | **4.0** | **15.4** | **44.2** | **14.8** |
| Min, max | 0.0, 169.9 | 2.2, 170.1 | 24.2, 47.5 | 3.0, 106.9 |

**$P$<0.001, difference from placebo.
CLB, clobazam; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance periods; VPA, valproate.

### Safety

- The most common treatment-emergent adverse events (any dose of FFA vs combined placebo groups in the double-blind studies) were fatigue (38.5%, 15.5%), somnolence (28.7%, 8.3%), lethargy (33.6%, 10.7%), and appetite suppression and hypophagia (36.9%, 8.3%) (**Table 2**)
- No valvular heart disease or pulmonary arterial hypertension was observed in any patient at any time

**Table 2. Most Common TEAEs During Double-Blind Treatment Period**

| Adverse Event | Placebo, n (%) (n=84) | Any Dose FFA, n (%) (n=122) |
|---|---|---|
| Appetite suppression, hypophagia | 7 (8.3) | 45 (36.9) |
| Somnolence | 7 (8.3) | 35 (28.7) |
| Sedation | 0 | 1 (0.8) |
| Fatigue | 13 (15.5) | 47 (38.5) |
| Lethargy | 9 (10.7) | 41 (33.6) |
| Behavioral abnormalities | 2 (2.4) | 12 (9.8) |
| Rash | 4 (4.8) | 8 (6.6) |
| Hypersensitivity reactions | 10 (11.9) | 15 (12.3) |
| Decreased blood sugar | 4 (4.8) | 9 (7.4) |

FFA, fenfluramine; TEAE, treatment-emergent adverse event.

## Conclusions

- FFA provided significant reductions in seizure frequency when added to common AED regimens, which included use of stiripentol, clobazam, valproate, or clobazam/valproate
- FFA was generally well tolerated
- There was no evidence of cardiotoxicity, with no cases of valvular heart disease or pulmonary arterial hypertension reported in any patient at any time

## References


1. Gataullina S, Dulac O. *Seizure*. 2017;44:58-64.
2. Dravet C. *Dev Med Child Neurol*. 2011;53(Suppl 2):1-6.
3. Boyd B, et al. *Int J Clin Pharmacol Ther*. 2019;57(1):11-9.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