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Fintepla® (Fenfluramine HCl Oral Solution) Provides Long-Term Clinically Meaningful Reduction in Seizure Frequency: Results of an Open-Label Extension Study

ZOGENIX

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INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, treatment-resistant epileptic encephalopathy
- In two recently completed phase 3, double-blind, placebo-controlled clinical studies, fenfluramine (FFA) demonstrated superior efficacy compared with placebo for the reduction in convulsive seizure frequency in children and young adults (2-18 years old) with DS[1,2]
- Upon completion of any of the program's phase 3 studies, patients were eligible to enroll in a long-term, open-label extension (OLE) study (NCT02823145)

METHODS

- All patients began the OLE study at a FFA dose of 0.2 mg/kg/day added to their current antiepileptic drug regimen regardless of their original treatment (FFA or placebo) or doses in the core studies
  - After 4 weeks, the FFA dose could be flexibly titrated up to a maximum of 0.8 mg/kg/day (with a maximum dose of 30 mg/day), or in patients concomitantly receiving stiripentol, up to a maximum dose of 0.5 mg/kg/day (with a maximum dose of 20 mg/day)
- Effectiveness was assessed using the baseline convulsive seizure frequency recorded prior to initiation of each patient's treatment in the double-blind core study
- Effectiveness and tolerability were assessed at Months 1, 2, and 3, and thereafter at 3-month intervals

RESULTS

- A total of 232 patients have enrolled in the OLE study as of March 13, 2018, the interim cutoff date, and had at least 1 dose of study drug and 1 month of diary data in the OLE
  - A total of 16 patients enrolled in the OLE study after participation in the drug-drug interaction pharmacokinetic portion of one of the core clinical studies (Study 1504, Cohort 1; NCT02926898). Because frequency of convulsive seizures was not assessed for this cohort of patients in the core clinical study, their results were not included in the assessment of effectiveness analyses of the OLE study but are included in the safety analyses
- Demographics are presented in **Table 1**
  - 128 (55.2%) were male
  - The mean age was 9.1±4.7 years

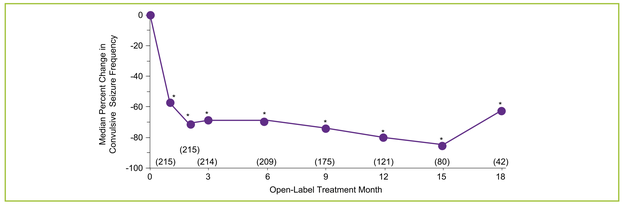
Table 1. Patient Demographics

N	232
Age, years: mean±SD (median) Min, max	9.1±4.7 (9.0) 2, 19
Age group, n (%) <6 years 6-18 years >18 years	 65 (28.0) 166 (71.6) 1 (0.4)
Sex, n (%) Male Female	 128 (55.2) 104 (44.8)
Race, n (%) White Black or African American Asian American Indian or Alaska Native Other Not reported*	 172 (74.1) 1 (0.4) 9 (3.9) 2 (0.9) 13 (5.6) 35 (15.1)
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino Not reported* Unknown*	 23 (9.9) 159 (68.5) 47 (20.3) 3 (1.3)
Region Canada or US Rest of world	 111 (47.8) 121 (52.2)
Baseline BMI, kg/m^2 Mean±SD (median) (min, max)	 17.9±4.2 (17.0) (11.8, 39.7)
Baseline convulsive seizure frequency per 28 days Median (min, max)[†]	 19.7 (0, 1464)
Patient disposition	
Days of treatment with FFA in OLE Median (min, max)	 256 (58, 634)
Patients discontinuing treatment n (%) Reasons Lack of efficacy Patient/caregiver withdrawal Adverse event Death (SUDEP) Physician decision	 22 (9.5) 16 3 1 1 1

*Privacy laws in some regions/countries preclude disclosure of certain personal information.
[†]Determined during the core study; does not include patients from Study 1504 Cohort 1.
SUDEP, sudden unexpected death in epilepsy.

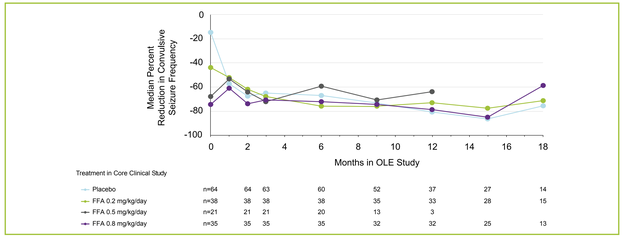
- FFA provided a clinically meaningful reduction in convulsive seizure frequency at Month 1 of the OLE study, and this response was maintained throughout the first 18 months of the OLE treatment period (**Figure 1**)
  - Over the entire OLE interim analysis period (median 256 days), the median decrease in convulsive seizure frequency was -66.8% (range, -100%, 234.9%; P<0.001 [Wilcoxon signed rank test])
- Long-term clinically meaningful improvements in convulsive seizure frequency were noted in patients enrolled in the OLE study from each treatment group in the core clinical studies, including in those patients originally treated with placebo (**Figure 2**)

Figure 1. Effect of FFA on Convulsive Seizure Frequency in Patients with DS Over the First 18 Months of the OLE Study



The number of patients assessed at each time point is shown in parentheses. Each point represents the cumulative change in seizure frequency from the start of the OLE, up to that time point, as compared with baseline seizure frequency. The decrease in patient number is primarily due to staggered entry into the study and not due to patient withdrawal.
*P<0.001 change from baseline (Wilcoxon signed rank test).

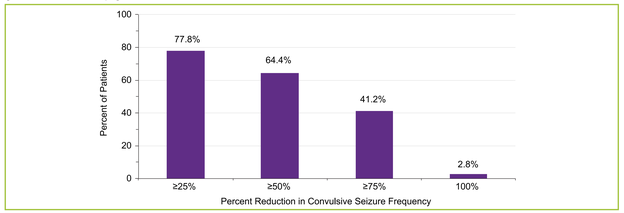
Figure 2. Percent Reduction in Convulsive Seizure Frequency Based on RCT Dose Group



Note that 58 patients who enrolled in the OLE study came from still ongoing randomized clinical studies and are not included in this figure because their treatment assignments are still blinded. Each point represents the cumulative change from baseline up to that time. The decrease in patient number is primarily due to staggered entry into the study and not due to patient withdrawal.
RCT, randomized, controlled trial.

- The majority of patients responded to FFA over the entire OLE interim analysis period (median 256 days) (**Figure 3**)
  - 64.4% of patients demonstrated clinically meaningful (≥50%) reduction in convulsive seizure frequency
  - 41.2% of patients demonstrated profound (≥75%) reduction in convulsive seizure frequency

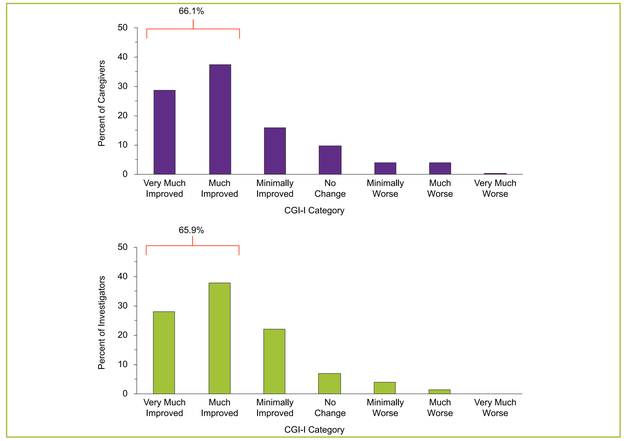
Figure 3. Responder Rates for Patients With DS Treated With FFA Over Entire OLE Study Period (Median 256 Days)



Individual patient percent reduction in convulsive seizure frequency was calculated for each patient's entire time in the OLE.

- Based on the most current assessments of Clinical Global Impression of Improvement (CGI-I) in the interim analysis period (median 256 days) of the OLE, 66.1% of caregivers and 65.9% of investigators rated their patients as "Much Improved" or "Very Much Improved" (**Figure 4**)

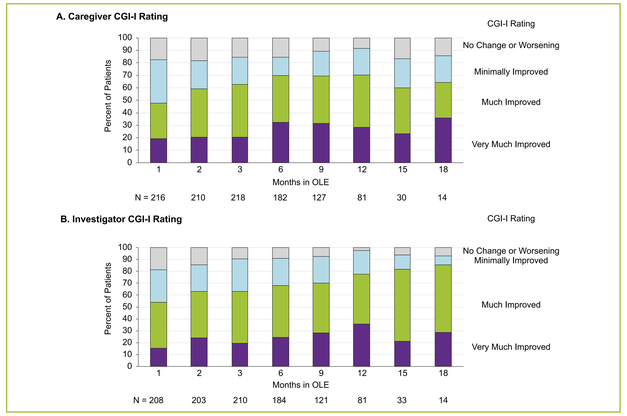
Figure 4. CGI-I as Rated by Caregivers (A) and Investigators (B)



CGI-I ratings in this figure are based on the most current assessment for each patient in the OLE (N=216).

- Clinically meaningful improvements in both caregiver and investigator CGI-I ratings were seen at Month 1 and were sustained throughout the OLE study (**Figure 5**)

Figure 5. CGI-I Over Time in the OLE Study



The decrease in patient number is primarily due to staggered entry into the study and not due to patient withdrawal.

Safety

- Adverse events occurring with a frequency ≥10% of patients are shown in **Table 2**
- The effects of FFA on appetite and body weight are shown in **Table 3**
- ECHO revealed no patient had developed valvular heart disease or pulmonary hypertension as of the interim analysis cutoff date of March 13, 2018

Table 2. Adverse Events Occurring in ≥10% of Patients During the Interim Analysis Period of the OLE

Adverse event	n (%)
Pyrexia	50 (21.6)
Nasopharyngitis	45 (19.4)
Decreased appetite	37 (15.9)
Influenza	27 (11.6)
Diarrhea	25 (10.8)
Upper respiratory tract infection	24 (10.3)

Table 3. Effects of FFA on Body Weight and Appetite in the Interim Analysis Period of the OLE

Event	n (%)
TEAE of appetite decreased/loss of appetite Resolution during OLE*	37 (15.9) 19 (51.4)
TEAE of weight loss	12 (5.2)
Patients who lost >7% of body weight since baseline Weight loss abated during OLE*	31 (13.4) 13 (41.9)

*Reflects resolution prior to the cutoff date for the interim analysis. Percentages are based on the number of patients with the adverse event.
TEAE, treatment-emergent adverse event.

CONCLUSIONS

- FFA provided a sustained clinically meaningful reduction (-66.8%) in convulsive seizure frequency during the entire OLE study period (median 256 days)
  - A clinically meaningful (≥50%) reduction in convulsive seizure frequency was observed in 64.4% of patients
  - A profound (≥75%) reduction in convulsive seizure frequency was observed in 41.2% of patients
- FFA was generally well tolerated as shown by the low withdrawal rate and adverse event profile consistent with what was observed in the randomized controlled studies
- No patient at any time developed valvular heart disease or pulmonary arterial hypertension

REFERENCES

1. Lagae L, et al. AES [poster 2.434], December 1-5, 2017; Washington, DC.
2. Zogenix announces positive top-line results from second pivotal phase 3 clinical trial of ZX008 in Dravet syndrome [press release]. Emeryville, CA, July 12, 2018.

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 Edward Weselcouch, PhD, and Barbara Schwedel, MS, of PharmaWrite (Princeton, NJ, USA) and were funded by Zogenix, Inc.

DISCLOSURES

LL: Received grants, personal fees, and other as a consultant/speaker from Zogenix during the conduct of the study; other as a consultant/speaker from LivaNova, grants and other as a consultant/speaker from UCB, other as a speaker from Shire, and other as a speaker from Eisai outside the submitted work. LL and the KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by the KU Leuven University/Antwerp University Hospital.

JS: Grants, travel support, Zogenix; Advisory board member, Dravet Syndrome Foundation; Reviewer, Epilepsy Study Consortium; Consultant fees, Epygenix.

RN, MP: Research funding, Zogenix.

GF, BSG, GM, ARG, AM: Employee, Zogenix; Stock ownership, Zogenix.

ML: Consultant, Zogenix.

Presented at the American Epilepsy Society (AES) Annual Meeting, November 30–December 4, 2018, New Orleans, LA