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Fintepla® (Fenfluramine HCl Oral Solution) Reduces Convulsive Seizure Frequency in Dravet Syndrome Patients Receiving an Antiepileptic Drug Treatment Regimen Containing Stiripentol: A Phase 3, Randomized, Placebo-Controlled Clinical Study

Rima Nabbout[1]; Stéphane Auvin[2]; Sameer Zuberi[3]; Nathalie Villeneuve[4]; Antonio Gil-Nagel[5]; Rocio Sanchez-Carpintero[6]; Ulrich Stephani[7]; Linda Laux[8]; Elaine Wirrell[9]; Kelly Knupp[10]; Catherine Chiron[11]; Gail Farfel[12]; Bradley S. Galer[12]; Glenn Morrison[12]; Michael Lock[12]; Arun Mistry[12]

[1]Hôpital Universitaire Necker - Enfants Malades, Service de Neurologie Pédiatrique Centre de Référence Épilepsies Rares (CReER), Paris, France; [2]Robert Debré University Hospital & Paris-Diderot University, Paris, France; [3]Paediatric Neurosciences Research Group, Royal Hospital for Children Glasgow, Glasgow, UK; [4]APHM, Department of Pediatric Neurology, Hôpital de la Timone, Marseille, France; [5]Hospital Ruber Internacional, Madrid, Spain; [6]Clínica Universidad de Navarra, Pediatric Neurology Unit, Pamplona, Spain; [7]Department of Neuropediatrics, Christian-Albrechts-University, Kiel, Germany; [8]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Children's Hospital Colorado, Department of Pediatrics and Neurology, University of Colorado – Anschutz Campus, Aurora, CO, USA; [11]Pediatric Neurology, Necker-Enfants Malades Hospital, Inserm U1129, Paris, France; [12]Zogenix, Inc., Emeryville, CA, USA

INTRODUCTION

- Dravet syndrome (DS) is a severe developmental and epileptic encephalopathy (incidence, ~1:15,700) that presents in the first 1-18 months of life with frequent, treatment-refractory convulsive seizures[1-4]
- Results from a recent phase 3 clinical study (Study 1) showed that fenfluramine (FFA) significantly reduced mean monthly convulsive seizure frequency (MCSF)[5]
  - Patients receiving stiripentol (STP) were not included in this study
  - The mean percent difference from placebo in reduction in mean MCSF was 63.9% for the FFA 0.8 mg/kg/day treatment group
  - The odds of achieving a clinically meaningful (≥50%) reduction in MCSF were 29 and 10 times higher in the FFA 0.8 mg/kg/day and 0.2 mg/kg/day groups than in the placebo group
  - The odds of achieving a profound (≥75%) reduction in MCSF were 50 and 10 times higher in the FFA 0.8 mg/kg/day and 0.2 mg/kg/day groups than in the placebo group
- This study (Study 1504) reports the results of a second phase 3 clinical study comparing FFA to placebo in patients with DS who had poor seizure control on an antiepileptic drug (AED) regimen that included STP
  - FFA was dosed at 0.5 mg/kg/day to approximate the systemic exposure of 0.8 mg/kg/day without STP

OBJECTIVE

- To determine the efficacy and safety of add-on FFA in patients with treatment-refractory DS receiving an AED regimen that included STP in a phase 3, double-blind, placebo-controlled clinical study (NCT02926898)

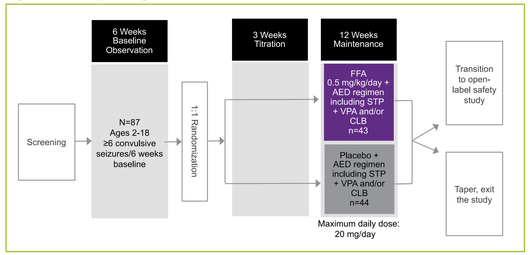
METHODS

Patients

- Key inclusion criteria
  - Children and young adults (ages 2 to 18 years, inclusive) with a diagnosis of DS
  - Stable AED regimen (≥4 weeks; could include ketogenic diet and/or vagus nerve stimulation) that included STP, as well as clobazam (CLB) and/or valproic acid (VPA)
  - ≥6 convulsive seizures (tonic-clonic, tonic, clonic) during the 6-week baseline period
- Key exclusion criteria
  - Pulmonary hypertension or current/past history of cardiovascular or cerebrovascular disease (eg, cardiac valve regurgitation, myocardial infarction, or stroke)
  - Concomitant treatment with cannabinoid products or modulators of serotonergic activity

Study Design

Figure 1. Study Design



AED, antiepileptic drug; FFA, fenfluramine; CLB, clobazam; STP, stiripentol; VPA, valproic acid.

Efficacy Outcomes

- Primary efficacy endpoint: FFA compared to placebo on the change in MCSF between baseline and the combined titration and maintenance (T+M) periods (**Figure 2**)
- Prespecified key secondary endpoints denoted with *
  - Proportion of patients who achieve ≥50% reduction from baseline in MCSF
  - Longest convulsive seizure-free interval (**Figures 3-7**)

Safety Outcomes

- Number of adverse events among placebo and FFA treatment groups
- Standardized color Doppler ECHO to monitor cardiac valve structure/function and pulmonary hypertension at screening, during treatment, and post-treatment

RESULTS

Patients

- Of 115 potential patients screened, 87 were randomized (n=44 placebo; n=43 FFA 0.5 mg/kg/day) and 77 completed the study (n=41 placebo; n=36 FFA 0.5 mg/kg/day)

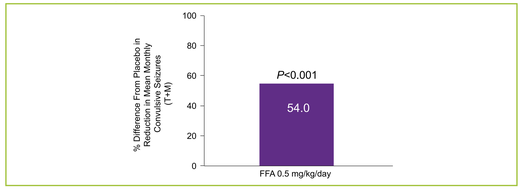
Table 1. Patient Baseline Characteristics

	Placebo	FFA 0.5 mg/kg/day	Overall
n	44	43	87
Age, years, mean±SD (min, max)	9.4±5.1 (2, 19)	8.8±4.6 (2, 18)	9.1±4.8 (2, 19)
Age group <6 years, n (%)	12 (27.3)	12 (27.9)	24 (27.6)
Male, n (%)	27 (61.4)	23 (53.5)	50 (57.5)
Race, n (%)			
Caucasian	29 (65.9)	23 (53.5)	52 (59.8)
Not reported[a]	11 (25.0)	13 (30.2)	24 (27.6)
BMI, kg/m^2, mean±SD	19.1±4.9	17.3±2.7	18.2±4.0
Convulsive seizure frequency per 28 days			
Median	10.7	14.0	
Mean±SD	21.6±27.7	27.9±36.9	
(min, max)	(3, 163)	(3, 213)	

[a]Not reported or missing; privacy laws in some regions/countries preclude disclosure of certain personal information.
BMI, body mass index; FFA, fenfluramine; SD, standard deviation.

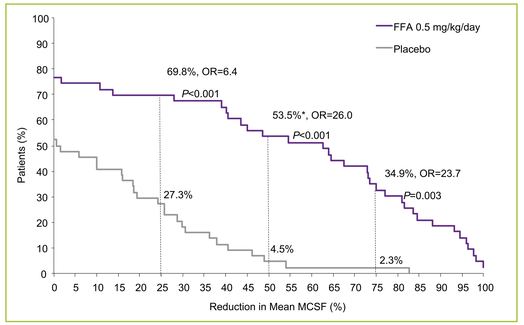
Efficacy

Figure 2. Primary Efficacy Endpoint: Reduction in Mean MCSF in FFA Treatment Group vs Placebo



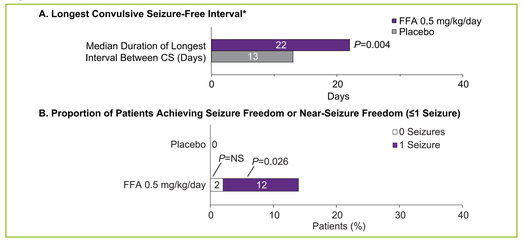
FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; T+M, combined titration and maintenance period.

Figure 3. Cumulative Response Curves for Percent Reduction in Mean MCSF From Baseline



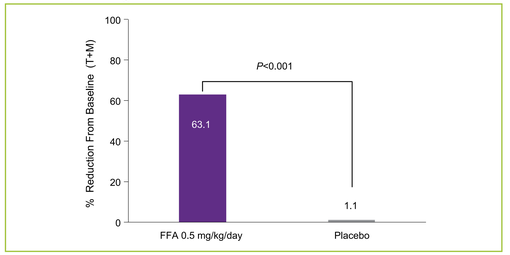
*Key secondary endpoint. *P* values are vs placebo. Results are plotted for combined T+M periods.
MCSF, monthly convulsive seizure frequency; OR, odds ratio vs placebo.

Figure 4. Seizure Freedom



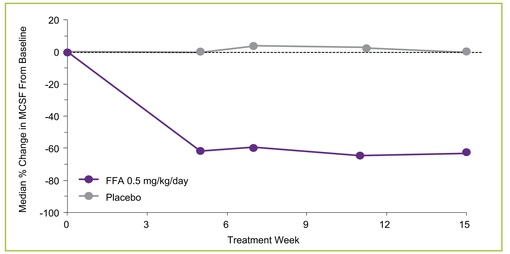
*Key secondary endpoint. CS, convulsive seizures; FFA, fenfluramine; NS, not significant.

Figure 5. Median Percent Reduction From Baseline in Convulsive Seizures Per 28 Days During Combined Titration and Maintenance Periods



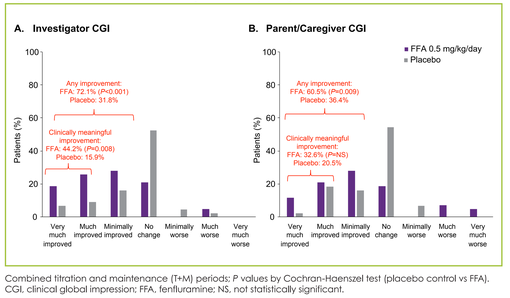
FFA, fenfluramine; T+M, combined titration and maintenance period.

Figure 6. Median Percent Change in MCSF Over Time



FFA, fenfluramine; MCSF, monthly convulsive seizure frequency.

Figure 7. Clinical Global Impression (CGI)



Combined titration and maintenance (T+M) periods; *P* values by Cochran-Haenszel test (placebo control vs FFA).
CGI, clinical global impression; FFA, fenfluramine; NS, not statistically significant.

Safety (Table 2)

- Prospective cardiac monitoring throughout the study demonstrated that all patients had normal mitral and aortic valve function at every visit
  - No cases of US FDA-defined cardiac valvulopathy or pulmonary hypertension were observed in any patient at any time during the study

Table 2. Most Common (≥10%) Non-Cardiovascular TEAEs in Any Treatment Group

	Placebo (n=44)	FFA 0.5 mg/kg/day (n=43)
Patients with ≥1 TEAE, n (%)	42 (96)	42 (98)
Patients with ≥1 serious TEAE, n (%)	7 (16)	6 (14)
TEAEs in ≥10% of patients in any treatment group		
Decreased appetite	5 (11)	19 (44)
Pyrexia	4 (9)	11 (26)
Fatigue	2 (5)	11 (26)
Diarrhea	3 (7)	10 (23)
Nasopharyngitis	15 (34)	7 (16)
Blood glucose decreased	2 (5)	6 (14)
Lethargy	2 (5)	6 (14)
Bronchitis	2 (5)	5 (12)
Seizure	7 (16)	2 (5)

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

CONCLUSIONS

- FFA (0.5 mg/kg/day) demonstrated robust efficacy in this phase 3 study in patients with DS optimized on an AED regimen that included STP with CLB and/or VPA
  - The odds of experiencing a clinically meaningful (≥50%) and profound (≥75%) reduction in MCSF were 26 and 24 times higher, respectively, in patients with FFA vs placebo added to their STP regimen
- FFA was generally well tolerated, with the most common AEs being decreased appetite, pyrexia, and fatigue
- No echocardiographic signs of cardiac valvular heart disease or pulmonary hypertension were observed in any patient at any time
- FFA may represent an important and effective new treatment option for patients with DS who are receiving STP as part of their AED regimen

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DISCLOSURES

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