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Improved Everyday Executive Function With Fintepla® (Fenfluramine HCl Oral Solution): Results From a Phase 3 Study in Children and Young Adults With Dravet Syndrome

ZOGENIX

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INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, treatment-resistant epileptic encephalopathy with comorbid neurodevelopmental and motor abnormalities
- Antiepileptic drugs have often been associated with negative impacts on cognition
- In 2 recently completed, phase 3, double-blind, placebo-controlled clinical studies, fenfluramine (FFA) demonstrated efficacy for the reduction of convulsive seizures in children and young adults with DS[1]
- Here we present a post hoc analysis of the impact of FFA on caregiver-reported everyday executive function of their children with DS from Study 1

METHODS

- Patients with DS 2-18 years old were randomly assigned to placebo, FFA 0.2 mg/kg/day, or FFA 0.8 mg/kg/day following a 6-week baseline period to establish baseline cognition
- Patients were treated for 14 weeks (2-week titration, 12-week maintenance)
- The Behavior Rating Inventory of Executive Function (BRIEF®)[2] was administered at baseline and after 14 weeks of treatment by caregivers/parents of children ≥5 years old to assess for impacts of treatment on everyday executive function
  - Responses were mapped to the more current version of the instrument, the 60-item BRIEF®2[3]
  - This change allowed for analysis of 9 more stable and sensitive scales, 3 broad index scores, and a Global Executive Composite (GEC) score (**Figure 1**)
  - Also allowed the use of Reliable Change Indices (RCIs)
    - The RCI in response to treatment is defined as a change in outcome (ie, BRIEF®2 scores) that is greater than that expected by chance, age, error, and psychometric reliability of the measure itself[4]
  - Raw scores were converted to T scores for analyses
    - T scores were based on a large (n=1400) standardization sample of parents and their children 5-18 years old matched by age, sex, race, parent education level, and geographic regions to recent nationwide population data
    - Percentages of cases in each treatment group showing improvement greater than the 90% confidence interval based on RCI were compared with likelihood ratios
    - Percentages of cases in each treatment group that showed worsening greater than the 80% confidence interval based on RCI were compared with likelihood ratios
    - Significance was set at $P<0.05$

Figure 1. BRIEF®2 Clinical Scales and Indexes – Caregiver/Parent Report Form

BRIEF®2 Clinical Scales and Indexes – Caregiver/Parent Report Form	
Behavior Regulation Index (BRI)	**Captures the child's ability to regulate and monitor behavior effectively.**
Inhibit	Control impulses; appropriately stop own behavior at the proper time.
Self-Monitor	Recognize the effect of own behavior on others.
Emotion Regulation Index (ERI)	**Represents the child's ability to regulate emotional responses and to shift, set, or adjust to changes in environment, people, plans, or demands.**
Shift	Move freely from one situation, activity, or aspect of a problem to another as the situation demands; transition; solve problems flexibly.
Emotional Control	Modulate emotional responses appropriately.
Cognitive Regulation Index (CRI)	**Reflects the child's ability to control and manage cognitive processes and to problem solve effectively.**
Initiate	Complete schoolwork or chores in timely fashion; finish tests within time limits; work at a satisfactory pace.
Working Memory	Hold information in mind for the purpose of completing a task; stay with or stick to an activity.
Plan/Organize	Anticipate future events; set goals; develop appropriate steps ahead of time to carry out an associated task or action; carry out tasks in a systematic manner; understand and communicate main ideas or key concepts.
Task Monitor	Check work; assess performance during or after finishing a task to ensure attainment of goal.
Organization of Materials	Keep workspace, play areas, and materials in an orderly manner.
Global Executive Composite (GEC)	**An overarching summary score that incorporates all of the BRIEF clinical scales.**

RESULTS

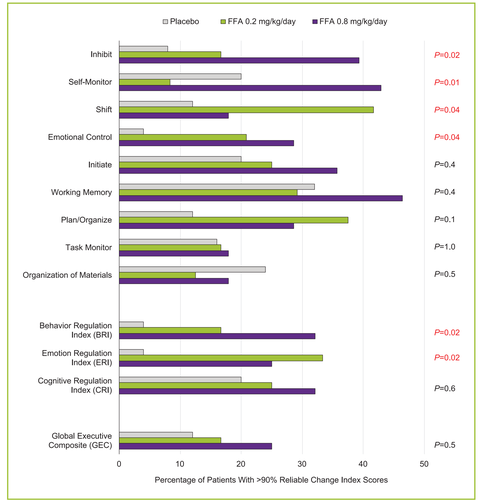
- A total of 77 patients had BRIEF® ratings during the study
  - Demographics are presented in **Table 1**
  - No significant differences among the 3 treatment groups in the distribution of sex, age, or race were observed

Table 1. Baseline Demographics

	Placebo	FFA 0.2 mg/kg/day	FFA 0.8 mg/kg/day	Total
N	25	24	28	77
Sex, n (%)				
Female	13 (52)	9 (38)	14 (50)	36 (47)
Male	12 (48)	15 (63)	14 (50)	41 (53)
Age group, years, n (%)				
5-7	8 (32)	4 (17)	10 (36)	22 (29)
8-10	5 (20)	10 (42)	6 (21)	21 (27)
11-13	2 (8)	1 (4)	6 (21)	9 (12)
14-18	10 (40)	9 (38)	6 (21)	25 (32)
Race, n (%)				
White	20 (80)	19 (79)	24 (86)	63 (82)
Asian	2 (8)	2 (8)	1 (4)	5 (6)
Native American	0 (0)	1 (4)	0 (0)	1 (1)
Not specified*	3 (12)	2 (8)	3 (11)	8 (10)

Total percentages in each category may not add up to 100% due to rounding.
*Privacy laws in some regions preclude disclosure of certain personal information.

Figure 2. Percentage of Patients in Each Treatment Group Showing a Clinically Meaningful Positive Change (Improvement) on BRIEF®2 >90% RCI



- A significant, clinically meaningful difference among the 3 treatment groups was shown on the inhibit, self-monitor, shift, and emotional control scales, as well as the Behavior Regulation Index (BRI) and Emotion Regulation Index (ERI) (**Figure 2**)
- A significant, clinically meaningful difference among the 2 treatment groups (FFA-pooled doses vs placebo) was shown on the inhibit, emotional control, and plan/organize scales, as well as the BRI and ERI (**Figure 3**)
- No significant, clinically meaningful differences among the treatment groups were observed with regard to worsening of everyday executive function (**Figure 4**)
- Odds ratio (OR) based on RCI >90% comparing the pooled FFA groups with placebo
  - BRI OR=8.0 (95% CI, 1.0 to 65.1)
  - ERI OR=9.7 (95% CI, 1.2 to 78.5)
  - Cognitive Regulation Index (CRI) OR=1.6 (95% CI, 0.5 to 5.1)

Figure 3. Percentage of Patients in the Active (FFA-Pooled Doses) and Placebo Treatment Groups Showing a Clinically Meaningful Positive Change (Improvement) on BRIEF®2 >90% RCI

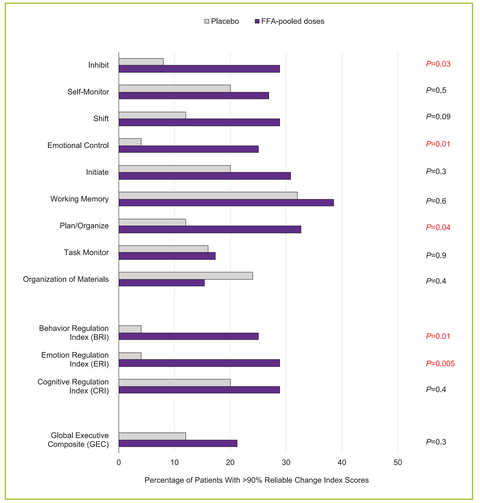
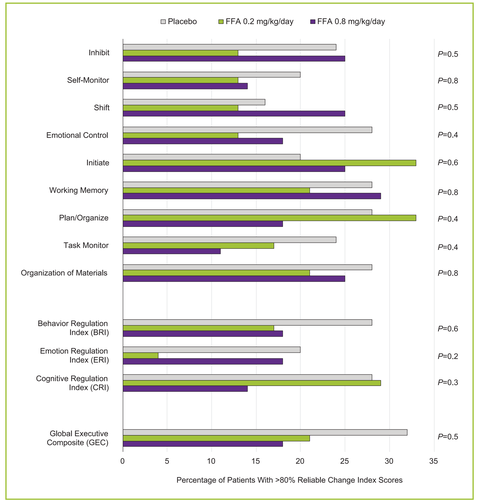


Figure 4. Percentage of Patients in Each Treatment Group Showing a Clinically Meaningful Negative Change (Worsening) on BRIEF®2 >80% RCI



CONCLUSIONS

- In children and young adults with DS, 14 weeks of treatment with FFA resulted in significant and clinically meaningful improvements in behavior regulation and emotion regulation, and some components of cognitive regulation (ie, plan/organize)
  - Behavior and emotion regulation serve as "building blocks" that enable higher-level cognitive regulation function
  - Children and young adults must be able to inhibit impulses, modulate emotions, and adapt flexibly to changes before they can demonstrate or develop cognitive regulatory functions, which include working memory, planning, and organization
- No significant, clinically meaningful differences were observed among the treatment groups for worsening of everyday executive function
- The impact of treatment with FFA on behavior and emotion regulation might be expected to enable improvements in the higher-level cognitive regulation with longer-term treatment
- These responses to FFA will continue to be examined in the long-term extension study (NCT02823145) to determine if everyday executive function continues to improve with longer-term treatment with FFA

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DISCLOSURES

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