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Relationships Between Self-Regulation and Quality of Life: Results From a Phase 3 Study of ZX008 (Fenfluramine HCl Oral Solution) 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 that is associated with neurodevelopmental abnormalities
- In a recent Phase 3 clinical trial, treatment with fenfluramine (administered as an oral solution of fenfluramine HCl containing 2.2 mg/mL fenfluramine) in patients with DS was associated with a substantial and statistically significant reduction in the frequency of convulsive seizures compared with placebo[1]
- In addition, fenfluramine was associated with improvements in executive control functions (ie, self-regulation) and quality of life (QOL)[1]
- Here we present an analysis of the relationship between caregiver-reported executive control functions and QOL ratings in children and young adults with DS who participated in the recent Phase 3 clinical trial

Methods

- Patients with DS aged 5 to 18 years were randomized to fenfluramine 0.7 mg/kg/day, fenfluramine 0.2 mg/kg/day, or placebo and were treated for 14 weeks
- The Pediatric Quality of Life Inventory™ (PedsQL™) 4.0 Generic Core Scales[2] and the Behavior Rating Inventory for Executive Function® (BRIEF®)[3] instruments were completed by caregivers at baseline and end of study
  - The BRIEF® responses were converted to the more current version of the instrument, the 60-item BRIEF®2[4]
- Spearman's Rho correlations were calculated to assess the associations between PedsQL™ Scales (Physical Functioning, Emotional Functioning, Social Functioning, School Functioning) and Summary scores (Physical Health, Psychosocial Health, and Total) or BRIEF®2 Indexes/Composite scores (Behavior Regulation Index [BRI], Emotion Regulation Index [ERI], Cognitive Regulation Index [CRI], and Global Executive Composite [GEC])
  - Higher scores on the PedsQL™ indicate better QOL
  - Lower scores on the BRIEF®2 Indexes/Composite indicate better executive control functions

Results

- PedsQL™ Scales/Summary scores and BRIEF®2 Indexes/Composite scores were available from caregivers of 73 patients enrolled in the clinical trial
  - PedsQL™ School Functioning Scale scores were available for 64 patients: one was missing baseline data, one was missing end of study data, and 7 were missing >50% of data, presumably because they do not go to school or have homework
- Baseline demographics are presented in **Table 1**

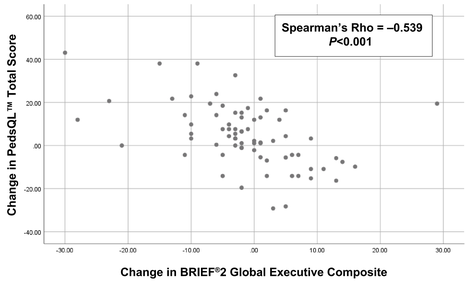
Table 1. Baseline Demographics

	Placebo (n=23)	FFA 0.2 mg/kg/day (n=23)	FFA 0.7 mg/kg/day (n=27)	Total (N=73)
Sex, n (%)				
Female	12 (52)	9 (39)	14 (52)	35 (48)
Male	11 (48)	14 (61)	13 (48)	38 (52)
Age, years				
Mean±SD (range)	11.7±4.4 (5-18)	10.7±3.7 (6-17)	9.9±4.0 (5-18)	10.6±4.1 (5-18)

FFA, fenfluramine.

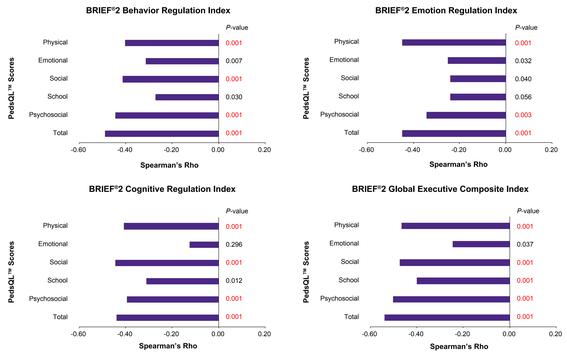
- Significant correlations between changes in PedsQL™ Scales/Summary scores and BRIEF®2 Indexes/Composite scores were observed in the entire study population
  - **Figure 1** presents an example of these correlations

Figure 1. Correlation Between Change in PedsQL™ Total Score and Change in BRIEF®2 Global Executive Composite



- Change in caregiver BRIEF®2 Indexes/Composite scores from baseline to end of study correlated with change in PedsQL™ Scales/Summary scores explaining 11% to 40% of the variance ($P<0.05$, **Figure 2**)

Figure 2. Correlations Between Change in PedsQL™ Scales/Summary Scores and Change in BRIEF®2 Indexes/Composite Scores



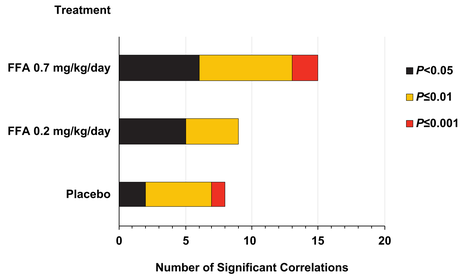
N=73, except for PedsQL™ School Scale (n=64).
P-values in red are statistically significant after Hochberg's adjustment for multiple comparisons.[5]

- The correlation between changes in BRIEF®2 Indexes/Composite scores from baseline to end of study with changes in PedsQL™ Scales/Summary scores in each treatment group are presented in **Figure 3**
  - Strong correlations ($P\leq0.01$) were more common in the fenfluramine 0.7 mg/kg/day group (n=9) than in the fenfluramine 0.2 mg/kg/day (n=4) or placebo (n=6) groups (**Figure 4**)

Figure 3. Correlation Between Change in BRIEF®2 Indexes/Composite Scores and Change in PedsQL™ Scales/Summary Scores by Treatment Group

•P<0.05, ••P≤0.01, •••P≤0.001 for correlation
n=23 for placebo and FFA 0.2 mg/kg/day, except for PedsQL™ School (n=20 for placebo and n=22 for FFA 0.2 mg/kg/day).
n=27 for FFA 0.7 mg/kg/day, except for PedsQL™ School (n=22).
No correction was made for multiple comparisons.
FFA, fenfluramine.

Figure 4. The Number of Significant Correlations Observed in Each Treatment Group for Change in BRIEF®2 Indexes/Composite Scores and Change in PedsQL™ Scales/Summary Scores



A total of 24 separate correlation analyses were done for each treatment.
No correction was made for multiple comparisons.
FFA, fenfluramine.

Conclusions

- Improvement in BRIEF®2 Indexes/Composite scores of self-regulation was associated with improvement in PedsQL™ Physical, Social, School, Psychosocial, and Total Scales/Summary scores
- An apparent dose response was observed, with a number of significant associations between changes in BRIEF®2 Indexes/Composite scores and PedsQL™ Summary scores
- The presence of the dose response suggests an important contribution of seizure control and/or an independent drug effect on self-regulation

References

1. Lagae L, et al. AES [poster 2.434]. December 1-5, 2017; Washington, DC.
2. Varni JW, et al. *Med Care*. 2001;39(8):800-12.
3. Gioia GA, et al. *Child Neuropsychol*. 2002;8(4):249-57.
4. Gioia GA, et al. *BRIEF®2: The Behavior Rating Inventory of Executive Function*. 2nd Ed. Lutz, FL: Psychological Assessment Resources, Inc.; 2015.
5. Hochberg Y. *Biometrika*. 1988;75(4):800-2.

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Disclosures

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AG, GMF, BSG, GM: Employees, Zogenix, Inc.; Ownership interest, Zogenix, Inc.
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