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# Profound Reduction in Seizure Frequency (≥75%) Leads to Improved Everyday Executive Function: Analysis From a Phase 3 Study of ZX008 (Fenfluramine HCI) in Children/Young Adults With Dravet Syndrome

## Kim I. Bishop<sup>1</sup>; Peter K. Isquith<sup>2</sup>; Gerard A. Gioia<sup>3</sup>; Glenn Morrison<sup>4</sup>; Arnold R. Gammaitoni<sup>4</sup>; Douglas Haney<sup>5</sup>; Rima Nabbout<sup>6</sup>; Elaine C. Wirrell<sup>7</sup>; Tilman Polster<sup>8</sup>; Joseph Sullivan<sup>9</sup>

<sup>1</sup>Global Pharma Consultancy, LLC, Muncy, PA, USA; <sup>2</sup>Boston Children's National Health System, Rockville, MD, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>4</sup>Zogenix, Inc., Emeryville, CA, USA; <sup>5</sup>Independent Statistical Consultant, Burlingame, CA, USA; <sup>5</sup>Independen <sup>6</sup>Hôpital Universitaire Necker - Enfants Malades, Paris, France; <sup>7</sup>Mayo Clinic, Rochester, MN, USA; <sup>8</sup>Mara Hospital, San Francisco, CA, USA

### Introduction

### **Dravet Syndrome and Executive Function**

- Patients with Dravet syndrome (DS) experience frequent pharmacoresistant seizures and deficits in executive function, an important aspect of emotional control, behavioral regulation, and cognition<sup>1-3</sup>
- Frequency and severity of convulsive seizures are likely to worsen executive functioning, although few long-term clinical studies are available to confirm<sup>4-6</sup>

### Fenfluramine as an Antiepileptic Drug

- In a recent randomized, double-blind, placebo-controlled phase 3 clinical study (Study 1)<sup>7</sup>:
- 50% of patients treated with fenfluramine (FFA) experienced profound  $(\geq 75\%)$  reduction in seizure frequency during the study period (14 weeks)
- FFA treatment resulted in significantly longer periods of seizure freedom
- Significant and clinically meaningful improvement was reported in executive function—behavior regulation, emotion regulation, and aspects of cognitive regulation
- In a recent long term open-label extension (OLE) study<sup>8</sup>:
- 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 ( $\geq$ 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

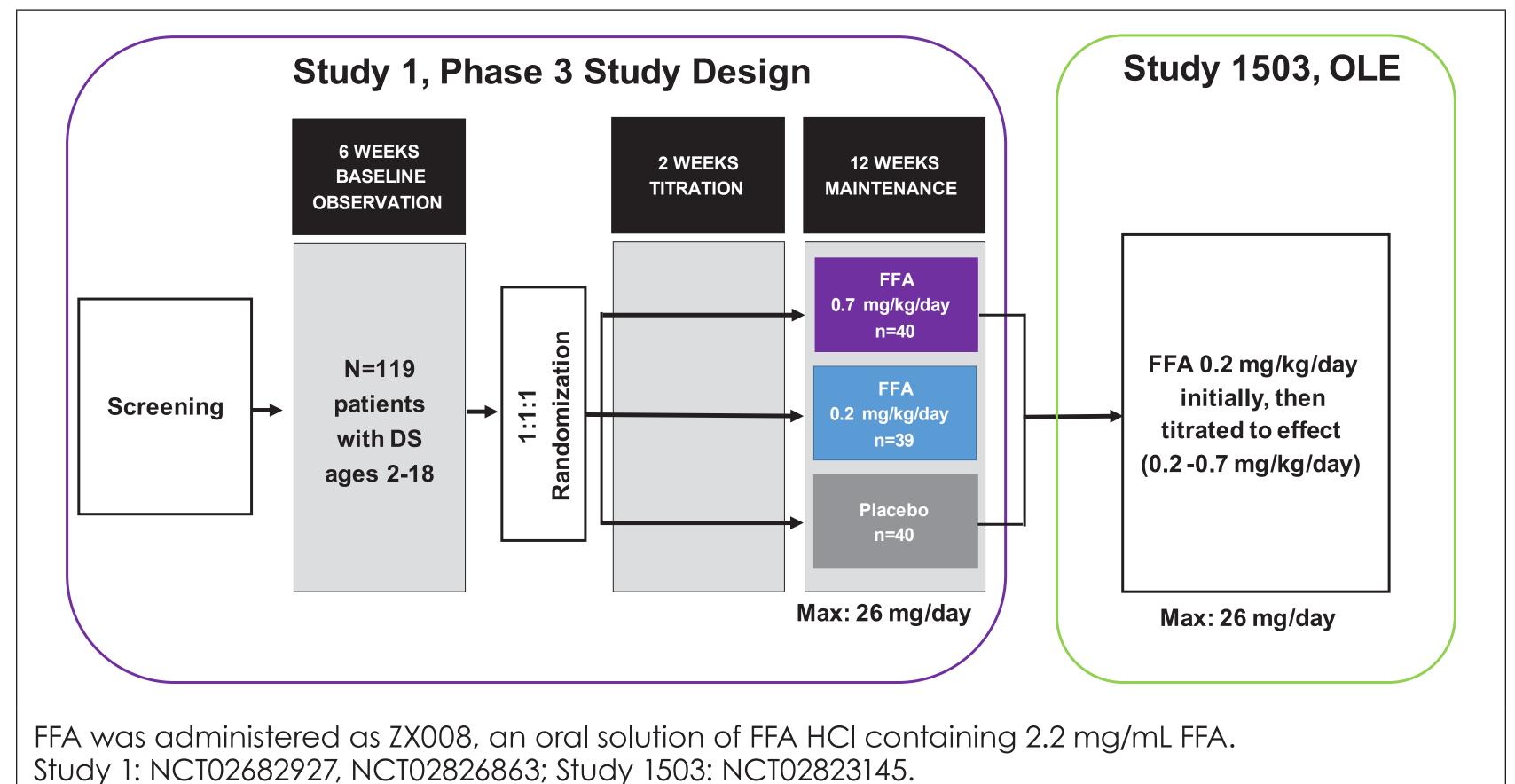
### **Objectives**

- To evaluate the relationship between changes in monthly convulsive seizure frequency (MCSF) and executive function in patients with DS after 1 year of treatment with add-on FFA
- Determine overall correlation between change in MCSF and changes in executive function
- Statistically compare executive function in patients who experienced profound (≥75%) compared to minimal (<25%) reductions in MCSF

### Methods

### Figure 1. Study Design

FFA, fenfluramine; OLE, open-label extension.



### Clinical Outcome Measures

- Convulsive seizure frequency per 28 days (hereafter, MCSF) was evaluated by handheld seizure e-diary
- MCSF reduction scores were calculated using the simple percentage difference in seizure frequency from pre-randomization baseline to Year 1 OLE
- Patients were subdivided into groups based on their level of MCSF reduction (<25% or ≥75%)
- The Behavior Rating Inventory of Executive Function (BRIEF®) Parent Form<sup>9</sup> was included as a safety endpoint and administered to caregivers/parents of patients with DS  $\geq$ 5 years old to assess for impacts of treatment on executive functions at pre-randomization baseline and after Year 1 of treatment
- Validated, standardized psychometric assessment instrument for quantifying a broad range of executive function components<sup>9</sup>
- Raw BRIEF<sup>®</sup>2 scores were transformed to T scores based on age- and sex-specific norms
- Lower scores on the BRIEF<sup>®</sup>2 indexes/composite scores, shown below in **Table 1**, correspond with better executive functioning

#### Table 1. Description of BRIEF<sup>®</sup>2 Indexes/Composite

Behavior Regu

**Emotion Regu** 

Cognitive Reg

Global Execu

### Statistical Analyses

- Correlations between percentage change in MCSF and change in BRIEF<sup>®</sup>2 indexes/composite from pre-randomization baseline to Year 1 were calculated using Spearman's Rho correlation coefficients (significance was set at P<0.05, two-tailed)
- Comparison of clinically meaningful change in BRIEF<sup>®</sup>2 Index/ Composite scores in patients with ≥75% vs <25% MSCF reduction was determined by Reliable Change Index (RCI)
- change'
- The proportion of patients with improvement in BRIEF<sup>®</sup>2 scores exceeding 95% RCI (≥10 T score points) was compared using a 2-sided Mann-Whitney U test with P<0.05 for the  $\geq$ 75% and <25% MCSF reduction groups

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- Responses were updated to the current 60-item BRIEF<sup>®</sup>2<sup>10</sup>
- T=50 represents the mean of the T score distribution

	Definition	
gulation Index (BRI)	Captures the child's ability to regulate and monitor behavior effectively	
ulation Index (ERI)	Represents the child's ability to regulate emotional responses and to shift, set, or adjust to changes in the environment, people, plans, or demands	
egulation Index	Reflects the ability to control and manage cognitive processes and problem solve effectively	
utive Composite	An overarching summary score that incorporates all of the BRIEF®2 clinical scales	

- RCI indicates when scores have changed beyond what is expected based on time and error alone, defined as "clinically meaningful
- The threshold for clinically meaningful change was defined as the level of change in BRIEF®2 T scores from baseline to Year 1 exceeding the RCI values with 95% certainty

## Results

### Patient Characteristics at Year 1 OLE

- (n=11/53; 21%) (**Table 2**)

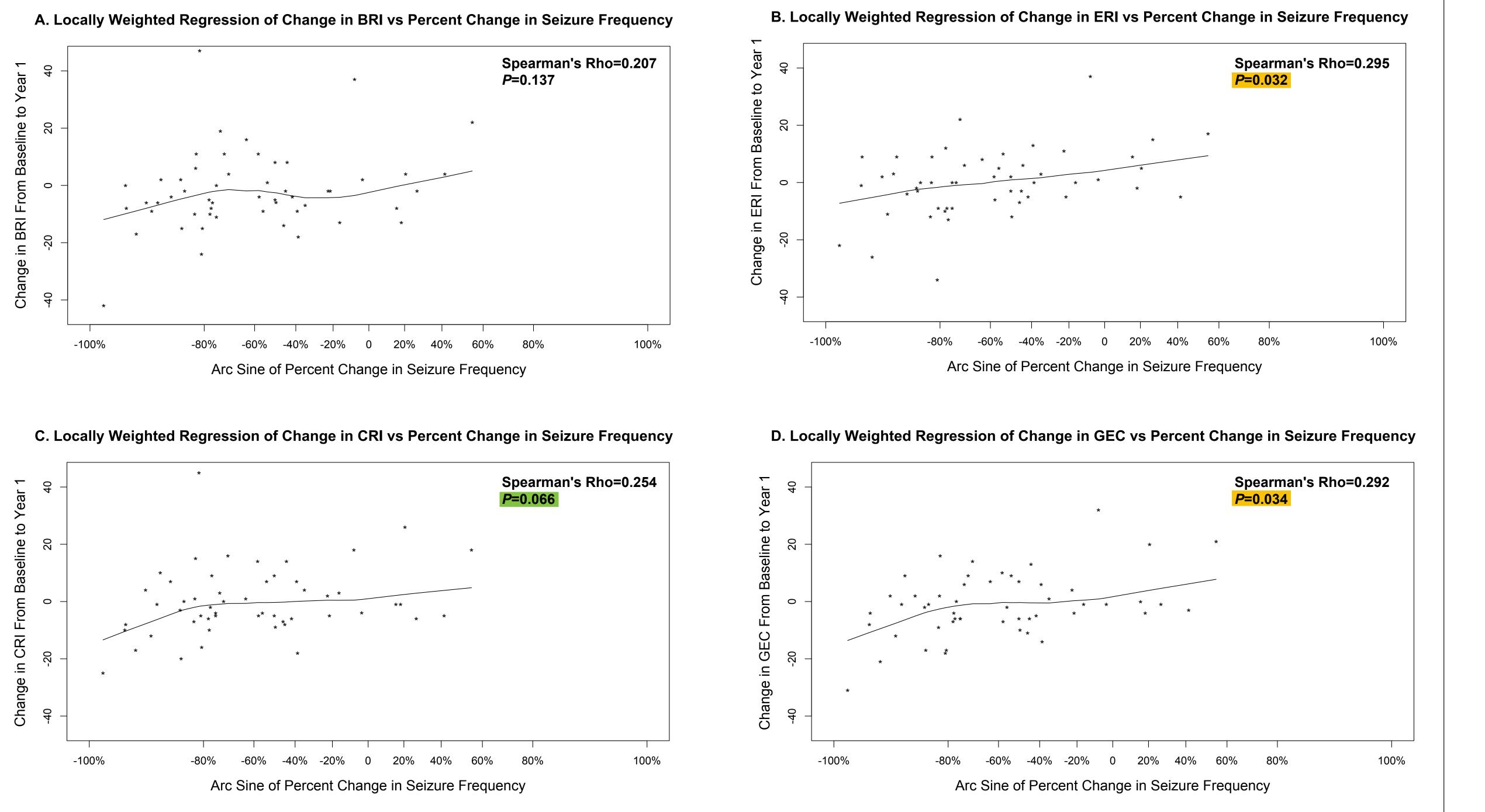
### Table 2. Patient Characteristics at Year 1 of the OLE

Characteristic
n (%)
Age (years), median (range)
Sex, n (%)
Male
Female
T score at baseline, median (range
BRI

<sup>a</sup>T=60-64, mildly impaired; T=65-69, potentially clinically impaired; T≥70, clinically impaired or clinically significant. BRI, Behavior Regulation Index; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; FFA, fenfluramine; GEC, Global Executive Composite score; MCSF, monthly convulsive seizure frequency.

#### Relationship Between Change in MCSF and Executive Function

#### Figure 2. Correlation Between Percentage Change in MCSF and Change in BRIEF<sup>®</sup>2 (A) BRI, (B) ERI, (C) CRI, and (D) GEC Scores From Baseline to Year 1 (N=53)



BRI, Behavior Regulation Index; ERI, Emotion Regulation Index; CRI, Cognitive Regulation Index; GEC, Global Executive Composite score.

• At analysis, 53 patients (30 males and 23 females, aged 5-18 years, mean age 11±4 years) in the OLE had completed ≥1 year of FFA and had both pre-randomization baseline and Year 1 BRIEF®2 data At Year 1, more patients (n=24/53; 45%) achieved profound (≥75%) vs minimal (<25%) levels of MCSF reduction</li>

MCSF Reduction Subgroup				
	<25%	≥75%	<b>Total Population</b>	
	11 (21)	24 (45)	53 (100)	
	9 (6-18)	12 (5-18)	10 (5-18)	
	5 (45)	14 (58)	30 (57)	
	6 (55)	10 (42)	23 (43)	
	74 (41-84)	68 (37-90)	69 (37-90)	
	57 (41-76)	57 (41-76)	61 (39-90)	
	69 (40-83)	60 (39-85)	61 (39-85)	
	69 (39-78)	66 (37-90)	66 (37-90)	

• Change in MCSF was significantly associated with improved ERI (P=0.032) and GEC (P=0.034) scores, with a trend toward improvement for CRI (P=0.066) and no statistical significance associated with BRI (P=0.137) (Figure 2)

### Comparison of Profound (≥75%) vs Minimal (<25%) MCSF Reduction

(*P*<0.05) (**Figure 3**)

#### Figure 3. Proportion of Patients With Significant, Clinically Meaningful Improvements (>95% RCI = ≥10-Point Change in T Scores) in BRIEF<sup>®</sup>2<sup>a</sup> Index/Composite Scores (Pre-Randomization Baseline to Year 1)

### Conclusions

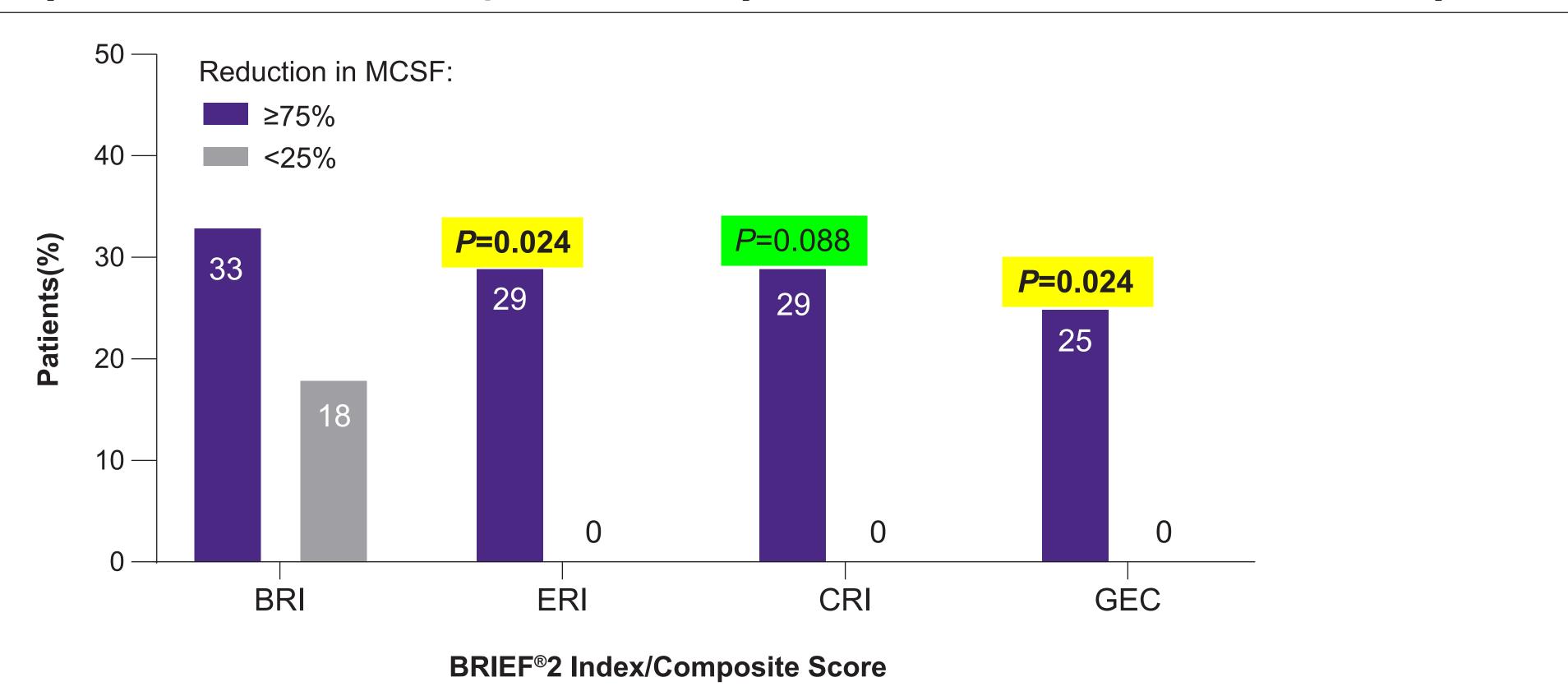
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 A significantly higher percentage of patients in the profound (≥75%) responder group experienced significant, clinically meaningful improvements (>95% RCI = ≥10-point change in T scores) on ERI and GEC



<sup>o</sup>Test statistics were not corrected for ties. Grouping variable: change in MCSF <25% vs ≥75%.

MCSF, monthly convulsive seizure frequency; BRI, Behavior Regulation Index; ERI, Emotion Regulation Index; CRI, Cognitive Regulation Index; GEC, Global Executive Composite score.

Reduction in MCSF was associated with improvement in overall executive function

• Patients who had profound reduction in MCSF (≥75%) were significantly more likely to show clinically meaningful improvements in overall executive function than patients who had minimal reduction in MCSF (<25%)

• Greater reduction in seizure frequency for prolonged periods of time (≥1 year) may improve some of the everyday executive function deficits experienced by patients with DS • Treatments capable of producing profound reduction in MCSF earlier in disease progression may

provide the greatest impact on executive function outcomes

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