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Fenfluramine treatment is associated with improvement in everyday executive function in preschool-aged children (<5 years) with Dravet syndrome: A critical period for early neurodevelopment

Kim I. Bishop [a,*], Peter K. Isquith [a,b], Gerard A. Gioia [a,c], Kelly G. Knupp [d], Ingrid E. Scheffer [e], Rima Nabbout [f], Nicola Specchio [g], Joseph Sullivan [h], Stéphane Auvin [i,j], J. Helen Cross [k], Renzo Guerrini [l], Gail Farfel [m], Bradley S. Galer [m], Arnold R. Gammaitoni [m]

[a] Global Pharma Consultancy, LLC, Muncy, PA, USA
[b] Boston Children's Hospital, Harvard Medical School, Boston, MA, USA
[c] Children's National Health System, Rockville, MD, USA
[d] Children's Hospital Colorado, Aurora, CO, USA
[e] University of Melbourne, Austin and Royal Children's Hospitals, Florey Institute and Murdoch Children's Research Institute, Melbourne, Victoria, Australia
[f] Reference Centre for Rare Epilepsies, Hôpital Universitaire Necker-Enfants Malades, APHP, Member of EPICARE, Institut Imagine, Université Paris Cité, Paris, France
[g] Rar Bambino Gesù Children's Hospital IRCCS, Rome, Italy
[h] University of California San Francisco, Benioff Children's Hospital, San Francisco, CA, USA
[i] Robert Debré Children's Hospital, APHP, Université de Paris, Paris, France
[j] Institut Universitaire de France (IUF), Paris, France
[k] UCL NIHR BRC Great Ormond Street Institute of Child Health, London, UK
[l] Anna Meyer Children's Hospital, University of Florence, Florence, Italy
[m] Formerly Zogenix, Inc., now a part of UCB, Emeryville, CA, USA

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ABSTRACT

Objective: To evaluate whether fenfluramine (FFA) is associated with improvement in everyday executive function (EF)—self-regulation—in preschool-aged children with Dravet syndrome (DS).
Methods: Children with DS received placebo or FFA in one of two phase III studies (first study: placebo, FFA 0.2 mg/kg/day, or FFA 0.7 mg/kg/day added to stiripentol-free standard-of-care regimens; second study: placebo or FFA 0.4 mg/kg/day added to stiripentol-inclusive regimens). Everyday EF was evaluated at baseline and Week 14–15 for children aged 2–4 years with parent ratings on the Behavior Rating Inventory of Executive Function®—Preschool (BRIEF®-P); raw scores were transformed to T-scores and summarized in Inhibitory Self-Control Index (ISCI), Flexibility Index (FI), Emergent Metacognition Index (EMI), and Global Executive Composite (GEC). Clinically meaningful improvement and worsening were defined using RCI ≥ 90% and RCI ≥ 80% certainty, respectively. The associations between placebo vs FFA combined (0.2, 0.4, and 0.7 mg/kg/day) or individual treatment groups and the likelihood of clinically meaningful change in BRIEF®–P indexes/composite T-scores were evaluated using Somers'*d*; pairwise comparisons were calculated by 2-sided Fisher's Exact tests ($p \leq 0.05$) and Cramér's V.
Results: Data were analyzed for 61 evaluable children of median age 3 years (placebo, n = 22; FFA 0.2 mg/kg/day, n = 15; 0.4 mg/kg/day [with stiripentol], n = 10; 0.7 mg/kg/day, n = 14 [total FFA, n = 39]). Elevated or problematic T-scores (T ≥ 65) were reported in 55% to 86% of patients at baseline for ISCI, EMI, and GEC, and in ~33% for FI. Seventeen of the 61 children (28%) showed reliable, clinically meaningful improvement (RCI ≥ 90% certainty) in at least one BRIEF®-P index/composite, including a majority of the children in the FFA 0.7 mg/kg/day group (9/14, 64%). Only 53% of these children (9/17) also experienced clinically meaningful reduction (≥50%) in monthly convulsive seizure frequency, including 6/14 patients in the FFA 0.7 mg/kg/day group. Overall, there were positive associations between the four individual treatment groups and the likelihood of reliable, clinically meaningful improvement in all BRIEF®-P indexes/composite (ISCI, $p = 0.001$; FI, $p = 0.005$; EMI, $p = 0.040$; GEC, $p = 0.002$). The FFA 0.7 mg/kg/day group showed a greater likelihood of reliable, clinically meaningful improvement than placebo in ISCI (50% vs 5%; $p = 0.003$), FI (36% vs 0%; $p = 0.005$), and GEC (36% vs 0%; $p = 0.005$). For EMI, the FFA 0.7 mg/kg/day group showed a greater likelihood of reliable, clinically meaningful

* Corresponding author at: Global Pharma Consultancy, LLC, Muncy, PA 17756, USA.
E-mail address: kib@globalpharmaconsultancy.com (K.I. Bishop).

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improvement than the FFA 0.2 mg/kg/day group (29% vs 0%; $p = 0.040$), but did not meet the significance threshold compared with placebo (29% vs 5%; $p = 0.064$). There were no significant associations between treatment and the likelihood of reliable, clinically meaningful worsening ($p > 0.05$).

Significance: In this preschool-aged DS population with high baseline everyday EF impairment, FFA treatment for 14–15 weeks was associated with dose-dependent, clinically meaningful improvements in regulating behavior, emotion, cognition, and overall everyday EF. These clinically meaningful improvements in everyday EF were not entirely due to seizure frequency reduction, suggesting that FFA may have direct effects on everyday EF during the early formative years of neurodevelopment.

1. Introduction

Dravet syndrome (DS) is a developmental and epileptic encephalopathy (DEE) characterized by multiple seizure types. This rare condition is commonly accompanied by intellectual disabilities, behavior problems, and limited adaptive functioning [1]. Pathogenic variants in *SCN1A*—the gene encoding the alpha-1 subunit of the $Na_v1.1$ sodium channel—lead to seizures and nonseizure comorbidities [2,3]. In their preschool years, many children with DS develop deficits in everyday executive function (EF) [4–6]—defined as self-regulatory abilities that guide, direct, and manage behavior, emotion, and cognition in everyday life [7–9]. Acquiring these EFs early in development is foundational to later cognitive, emotional, and behavioral processes [10]. Disruptions in the early development of everyday EF due to epilepsy can have a negative impact on the overall quality of life and lead to poor adaptive functioning later in life [11,12]. Therefore, early intervention to reduce EF deficits is increasingly recognized as an important clinical objective for treating children with epilepsy [13–16].

The Behavior Rating Inventory of Executive Function® (BRIEF®) family of instruments are the most widely used rating scales for assessing everyday EF [17], including in patients with drug-resistant epilepsies [18,19]. Previous analyses of the Behavior Rating Inventory of Executive Function®, Second Edition (BRIEF®2), observer-reported outcomes (ObsROs) showed that treatment with fenfluramine (FFA) was associated with reliable, clinically meaningful improvement in aspects of everyday EF in school-age children with DS at 14–15 weeks [20–26] and one year of treatment [27], and in patients with Lennox-Gastaut syndrome (LGS) at 14 weeks of treatment [28]. These post-hoc exploratory ("hypothesis-generating") analyses used data from double-blind, placebo-controlled, randomized controlled trials (RCTs) and open-label extension (OLE) studies, and evaluated everyday EF using the parent form of the BRIEF®2, validated for children and young adults aged 5 to 18 years [9,29]. However, these analyses did not evaluate everyday EF in the subset of younger children (<5 years) who participated in the RCTs.

FFA has dual serotonergic (5-hydroxytryptamine, 5-HT) and sigma-1 receptor (σ1R) mechanisms of action, including agonist activity at 5-HT_4 receptors and positive modulation of σ1R. Data from preclinical studies and clinical studies in healthy volunteers suggest that this unique pharmacology may mediate learning, memory, and behavioral effects related to cognitive performance [30–34]. These pharmacological mechanisms are unique among antiseizure medications (ASMs) [35]. In addition to the ability of FFA to reduce seizure frequency, these mechanisms may play a direct role in clinical outcomes in everyday EF in children and young adults with DS or LGS [20,21,27,28,33].

The preschool years (age $\leq$ 5 years) are a critical window for neurodevelopment, including the maturation and development of EFs [36–38]. In this study, we use pooled data from two RCTs to evaluate the effect of FFA treatment on everyday EF in preschool-aged children with DS. The objectives of this study were (1) to evaluate whether 14 to 15 weeks of FFA treatment was associated with the likelihood of reliable clinically meaningful improvement in everyday EF relative to placebo in children with DS aged < 5 years, (2) to assess the associations between different dose levels of FFA treatment and the likelihood of reliable, clinically meaningful improvement in everyday EF during these early formative years of neurodevelopment, and (3) to evaluate whether FFA was associated with the likelihood of reliable, clinically meaningful worsening in everyday EF when added to a baseline standard-of-care regimen.

2. Methods

2.1. Patients

Data analyzed were from the cohort of patients with DS aged < 5 years who participated in one of two 14- to 15-week RCTs (NCT02682927/NCT02826863 and NCT02926898) [20,39]. In the first RCT, patients were randomized to receive placebo or FFA (0.2 mg/kg/day or 0.7 mg/kg/day) added to standard-of-care regimens that did not include stiripentol. In the second RCT, stiripentol was an inclusion criterion, and the dose of FFA was reduced from 0.7 mg/kg/day to 0.4 mg/kg/day (maximum, 17 mg/day) due to a known drug-drug interaction between stiripentol and FFA [40]. A dosage of FFA 0.4 mg/kg/day in stiripentol-containing regimens was characterized as having similar pharmacokinetics, efficacy, and safety profiles as FFA 0.7 mg/kg/day in stiripentol-free regimens [39,41]. For this analysis, data from the placebo groups of both studies were combined and the FFA 0.4 mg/kg/day group was analyzed as a separate group.

2.2. Statistical procedures

2.2.1. Assessment of everyday EF

Everyday EF was evaluated at baseline and at Weeks 14 to 15 via parent ratings on the Behavior Rating Inventory of Executive Function®—Preschool Version (BRIEF®–P) for children aged 2 to < 5 years [42]. BRIEF®–P raw scores were transformed to T-scores (mean T = 50 ± 10 SD) based on a parent normative sample of 460 neurotypical individuals [42]. Higher T-scores reflect greater difficulties in everyday EF, with age- and gender-adjusted T-scores $\geq$ 65, at ~93rd percentile, which is typically considered elevated or problematic [43]. T-scores were summarized for the Inhibitory Self-Control Index (ISCI) that reflects a young child's ability to modulate behavior and emotions, the Flexibility Index (FI) that reflects the ability to adapt to change behaviorally and emotionally, and the Emergent Metacognition Index (EMI) that reflects the ability to initiate, plan, organize, and sustain problem-solving, and the Global Executive Composite (GEC) that reflects overall everyday EF (or self-regulation). Real-world examples describing these indexes/composite are presented in Table 1.

Table 1
Assessment of Everyday Executive Function With the BRIEF®-P Parent Form: Real-World Examples and the Required Changes in T-Scores for Reliable, Clinically Meaningful Worsening (RCI ≥ 80% Certainty) or Improvement (RCI ≥ 90 and ≥ 95% Certainty) at Each Index/Composite.[a]

BRIEF®-P Indexes/ Composite	Real-World Examples	RCI Certainty Level		
		Worsening	Improvement	
		≥80% (Increase in T-scores)	≥90% (Decrease in T-scores)	≥95% (Decrease in T-scores)
Inhibitory Self-Control (ISCI)	Impulsive and emotionally reactive • Controlling impulses • Stopping a behavior when needed • Regulating emotions	≥ 6	≤ −8	≤ −9
Flexibility (FI)	Inflexible and not adaptive to new things, people, or situations and/or having strong emotional outbursts • Regulating or modulating emotional reactions • Moving flexibly or adaptively to new situations or activities	≥ 7	≤ −9	≤ −11
Emergent Metacognition (EMI)	Inattentive, distractible, and disorganized • Getting started on tasks or activities • Remaining attentive or staying focused • Holding information in active memory • Planning and organizing activities or work • Monitoring success in achieving a goal	≥ 8	≤ −10	≤ −12
Global Executive Composite (GEC)	Summary score that incorporates all five clinical scales that make up the three indexes (ISCI, FI, EMI)	≥ 7	≤ −9	≤ −10

BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version; RCI, Reliable Change Index.
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2.2.2. Patient characteristics

Patient characteristics and BRIEF®-P T-score distributions were tabulated and reported with descriptive statistics (proportions, means, medians, frequencies). Baseline BRIEF®-P T-score distributions were compared using nonparametric statistical tests (Mann-Whitney *U* or Kruskal-Wallis). Baseline proportions of elevated or problematic BRIEF®-P T-scores (≥65) between treatment groups were evaluated using the Chi-square statistic. Changes in seizure frequency at baseline in the RCT and at Weeks 14 to 15 were tabulated for the patients who completed the BRIEF®-P at both time points.

2.2.3. Reliable, clinically meaningful change

A Reliable Change Index (RCI) [44–46] evaluates reliable, clinically meaningful changes (improvement or worsening) in an individual's T-scores over time at different levels of certainty (Table 1). It is a well-accepted method for interpreting changes in neurocognitive and behavioral measures that indicate whether changes in scores are beyond what is expected based on practice effects, age, and reliability of the score [44–48]. RCI ≥ 90%, a more stringent criterion for detecting change than the commonly reported RCI ≥ 80% threshold [49], was used to compare reliable, clinically meaningful improvement (decrease in T-scores) in BRIEF®-P indexes/composite T-scores for each preschooler from baseline to Week 14 or 15 [42]. For consistency with prior reports (Bishop et al 2021 [27]), results using an even more rigorous threshold (RCI ≥ 95% certainty) are presented in **Supplemental Material**. RCI ≥ 80% certainty was used to compare reliable, clinically meaningful worsening (increase in T-scores) in BRIEF®-P indexes/composite T-scores for each preschooler from baseline to Week 14 or 15. The required changes in BRIEF®-P indexes/composite T-scores for clinically meaningful change (improvement or worsening) are presented in Table 1.

2.2.4. Analysis of change in everyday EF

Associations between placebo and the combined group of the three doses of FFA (0.2 mg/kg/day, 0.4 mg/kg/day [with stiripentol], and 0.7 mg/kg/day)—hereinafter referred to as "the placebo vs FFA combined treatment groups"—and the likelihood of reliable, clinically meaningful change (worsening or improvement) in

Table 2
Patient Demographics and Baseline Characteristics for Placebo vs FFA Combined (0.2 mg/kg/day, 0.4 mg/kg/day, and 0.7 mg/kg/day) Treatment Groups and the Four individual Treatment Groups (Placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], and FFA 0.7 mg/kg/day) (N = 61).

	Placebo	FFA combined (all doses)	FFA (0.2 mg/kg/day)	FFA (0.4 mg/kg/day) (with stiripentol)[a]	FFA (0.7 mg/kg/day)[a]
n	22	39	15	10	14
Age, years					
Mean (SD)	3.1 (0.9)	3.2 (0.8)	3.3 (0.9)	3.2 (0.8)	3.0 (0.9)
Median	3.0	3.0	4.0	3.0	3.0
Sex, n (%)					
Female	8 (36.4%)	20 (51.3%)	8 (53.3%)	6 (60.0%)	6 (42.9%)
Male	14 (63.6%)	19 (48.7%)	7 (46.7%)	4 (40.0%)	8 (56.1%)

FFA, fenfluramine.
[a] Due to a known drug-drug interaction, 0.4 mg/kg/day regimens with stiripentol result in levels of systemic FFA that are pharmacokinetically similar to FFA 0.7 mg/kg/day in regimens without stiripentol.

Table 3
Patient Baseline BRIEF®-P Indexes/Composite T-Scores for Placebo and FFA Combined (0.2 mg/kg/day, 0.4 mg/kg/day [with stiripentol], and 0.7 mg/kg/day) Treatment Groups and Four Individual Treatment Groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day, FFA 0.7 mg/kg/day) (N = 61).

Characteristic	Placebo (n = 22)		FFA combined (0.2, 0.4 [with stiripentol], and 0.7 mg/kg/day) (n = 39)		FFA, 0.2 mg/kg/day (n = 15)		FFA, 0.4 mg/kg/day (with stiripentol) (n = 10)		FFA, 0.7 mg/kg/day (n = 14)	
BRIEF®-P Indexes/ Composite	Baseline T-score, median (range)[a]	T ≥ 65 at baseline, n (%)[b]	Baseline T-score, median (range)[a]	T ≥ 65 at baseline, n (%)[b]	Baseline T-score, median (range)[a]	T ≥ 65 at baseline, n (%)[b]	Baseline T-score, median (range)[a]	T ≥ 65 at baseline, n (%)[b]	Baseline T-score, median (range)[a]	T ≥ 65 at baseline, n (%)[b]
Inhibitory Self-Control	69.5 (49–96)	12 (54.5%)	68 (41–100)	24 (61.5%)	68 (47–95)	9 (60.0%)	73 (42–87)	7 (70.0%)	67 (41–100)	8 (57.1%)
Flexibility	57.5 (40–92)	7 (31.8%)	58 (36–94)	13 (33.3%)	60 (36–86)	5 (33.3%)	56.5 (40–92)	4 (40.0%)	56.5 (42–94)	4 (28.6%)
Emergent Metacognition	79.5 (51–109)	19 (86.4%)	69 (39–109)	26 (66.7%)	74 (48–103)	10 (66.7%)	74.5 (60–96)	7 (70.0%)	67 (39–109)	9 (64.3%)
Global Executive Composite	71.5 (60–108)	18 (81.8%)	71 (40–111)	27 (69.2%)	74 (45–102)	9 (60.0%)	75.0 (50–93)	8 (80.0%)	67.5 (40–111)	10 (71.4%)

FFA, fenfluramine; BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version.
[a] No statistically significant differences in T-score distributions between placebo and FFA combined treatment groups calculated by Mann-Whitney *U* or the four individual treatment groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day (with stiripentol), or FFA 0.7 mg/kg/day) calculated by Kruskal-Wallis at baseline.
[b] No statistically significant differences in the proportion of elevated or problematic T-scores (≥65) between placebo and FFA combined treatment groups calculated by Chi-square or the four individual treatment groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], or FFA 0.7 mg/kg/day) calculated by Chi-square at baseline.

BRIEF®-P indexes/composite T-scores from baseline to Week 14 or 15 was evaluated via cross-tabulations and asymmetric Somers' delta, or Somers' *d*, a nonparametric measure of the strength and direction of association between ordinal variables [50]. When there was a significant association ($p \leq 0.05$), then two-sided Fisher's Exact tests were performed to determine whether the proportion of children showing clinically meaningful change in the two groups was significantly different ($p \leq 0.05$); if so, effect sizes were then reported as Cramér's V [51]. Cross-tabulations and Somers' *d* were also used to evaluate associations between placebo (FFA 0 mg/kg/-day), FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day (with stiripentol), and FFA 0.7 mg/kg/day—hereinafter referred to as "the four individual treatment groups"—and the likelihood of clinically meaningful change in BRIEF®-P indexes/composite T-scores from baseline to the end of the study. Two-sided Fisher's Exact tests were also performed following a significant association ($p \leq 0.05$) to determine whether the likelihood of clinically meaningful change in one of the four individual treatment groups differed significantly from another ($p \leq 0.05$); if so, effect sizes were then reported as Cramér's V. Due to the exploratory nature of this study, no corrections were made for multiple comparisons.

3. Results

3.1. Patient characteristics

Prerandomization baseline and end-of-study BRIEF®–P data were available to analyze for 61 of 72 total enrolled children aged 2 to 4 years (Table 2). Of the 61 patients with evaluable BRIEF®-P data, 8 patients withdrew early (**supplemental Figure S1**). The median age of the children was 3 years, with 54% males and 46% females (Table 2). A total of 22 children received placebo, whereas 39 children received FFA (0.2 mg/kg/day: n = 15; 0.4 mg/kg/day [with stiripentol]: n = 10; or 0.7 mg/kg/day: n = 14). At baseline, the majority of patients (55%-86%) scored in the range typically considered elevated or problematic (T-score ≥ 65) for ISCI, EMI, and GEC, with approximately 32% to 33% of patients scoring in the range typically considered elevated or problematic for FI (Table 3). No statistically significant differences in T-score distributions or the proportion of elevated or problematic T-scores (≥65) were observed between the placebo vs FFA combined treatment groups at baseline (Table 3). The four individual treatment groups also showed no statistically significant differences in T-score distributions or the proportion of elevated or problematic T-scores (≥65) at baseline.

3.2. Evaluation of clinically meaningful improvements in BRIEF®-P indexes/composite

A total of 17/61 (28%) individual children had reliable, clinically meaningful improvements in at least one BRIEF®-P index at the RCI ≥ 90% threshold (Table 4). The response was dose-dependent: 9/14 children (64%) in the FFA 0.7 mg/kg/day group achieved reliable, clinically meaningful improvements compared with 3/10 children (30%) in the FFA 0.4 mg/kg/day group (with stiripentol), 3/15 children (20%) in the FFA 0.2 mg/kg/day group, and 2/22 children (9%) in the placebo group (Fig. 1). Table 4 presents individual patient-level data for changes in seizure frequency and changes in T-score. Reliable, clinically meaningful improvements on BRIEF®-P indexes did not always correspond with clinically meaningful (≥50%) reduction in monthly convulsive seizure frequency (MCSF) (Table 4). Seven of 17 children (41%) achieved reliable, clinically meaningful improvement in at least 1 BRIEF®-P index without achieving ≥ 50% reduction in seizure frequency,

Table 4
Individual-Level Change in MCSF in 17/61 Preschool Patients with Dravet Syndrome Who Showed Reliable, Clinically Meaningful Improvement in ≥ 1 BRIEF®-P Index/Composite T-Scores at RCI ≥ 90% Certainty at the End of the RCT.

ID	Change in MCSF	Treatment Group	Index/ Composite	T-Score BL	T-Score RCT	Change in T-Score
1	−100.00	FFA 0.7 mg/kg/day	EMI	103	93	−10
2	−100.00	FFA 0.2 mg/kg/day	ISCI	52	43	−9
3	−100.00	FFA 0.7 mg/kg/day	EMI	66	49	−17
3	−100.00	FFA 0.7 mg/kg/day	GEC	52	40	−12
4	−96.56	FFA 0.7 mg/kg/day	ISCI	82	74	−8
5	−96.10	FFA 0.7 mg/kg/day	ISCI	60	50	−10
5	−96.10	FFA 0.7 mg/kg/day	FI	55	44	−11
5	−96.10	FFA 0.7 mg/kg/day	EMI	79	60	−19
5	−96.10	FFA 0.7 mg/kg/day	GEC	72	54	−18
6	−93.33	FFA 0.4 mg/kg/day[a]	ISCI	73	65	−8
6	−93.33	FFA 0.4 mg/kg/day[a]	EMI	94	80	−14
6	−93.33	FFA 0.4 mg/kg/day[a]	GEC	81	71	−10
7	−82.68	FFA 0.7 mg/kg/day	ISCI	100	76	−24
7	−82.68	FFA 0.7 mg/kg/day	FI	94	78	−16
7	−82.68	FFA 0.7 mg/kg/day	GEC	111	94	−17
8	−64.34	FFA 0.4 mg/kg/day[a]	ISCI	73	55	−18
8	−64.34	FFA 0.4 mg/kg/day[a]	EMI	78	61	−17
8	−64.34	FFA 0.4 mg/kg/day[a]	GEC	76	60	−16
9	−60.07	Placebo	ISCI	85	76	−9
10	−57.58	FFA 0.7 mg/kg/day	ISCI	67	53	−14
10	−57.58	FFA 0.7 mg/kg/day	FI	63	49	−14
10	−57.58	FFA 0.7 mg/kg/day	GEC	65	51	−14
11	−44.60	FFA 0.7 mg/kg/day	ISCI	79	64	−15
11	−44.60	FFA 0.7 mg/kg/day	FI	65	45	−20
11	−44.60	FFA 0.7 mg/kg/day	EMI	71	61	−10
11	−44.60	FFA 0.7 mg/kg/day	GEC	75	60	−15
12	−23.57	FFA 0.7 mg/kg/day	ISCI	63	55	−8
12	−23.57	FFA 0.7 mg/kg/day	FI	61	52	−9
13	−2.00	Placebo	EMI	79	66	−13
14	4.92	FFA 0.2 mg/kg/day	FI	59	45	−14
14	4.92	FFA 0.2 mg/kg/day	GEC	76	65	−11
15	29.55	FFA 0.7 mg/kg/day	ISCI	43	35	−8
16	51.65	FFA 0.2 mg/kg/day	ISCI	95	87	−8
16	51.65	FFA 0.2 mg/kg/day	FI	86	71	−15
17	53.87	FFA 0.4 mg/kg/day[a]	ISCI	82	63	−19
17	53.87	FFA 0.4 mg/kg/day[a]	FI	67	52	−15

BL, baseline; BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version; EMI, Emergent Metacognition Index; FFA, fenfluramine; FI, Flexibility Index; GEC, Global Executive Composite; ISCI, Inhibitory Self Control Index; MCSF, monthly convulsive seizure frequency; RCT, randomized controlled trial. Alternating shading identifies individual patients. T-scores T ≥ 65 are typically considered problematic. The thresholds for reliable, clinically meaningful changes in T-scores at RCI ≥ 90% were ≤ −8 for ISCI, ≤ −9 for FI, ≤−10 for EMI, and ≤ −9 for GEC, where negative numbers represent improvement.

[a] FFA 0.4 mg/kg/day regimens (with stiripentol) result in levels of systemic fenfluramine that are pharmacokinetically similar to FFA 0.7 mg/kg/day regimens without stiripentol due to known drug-drug interactions.

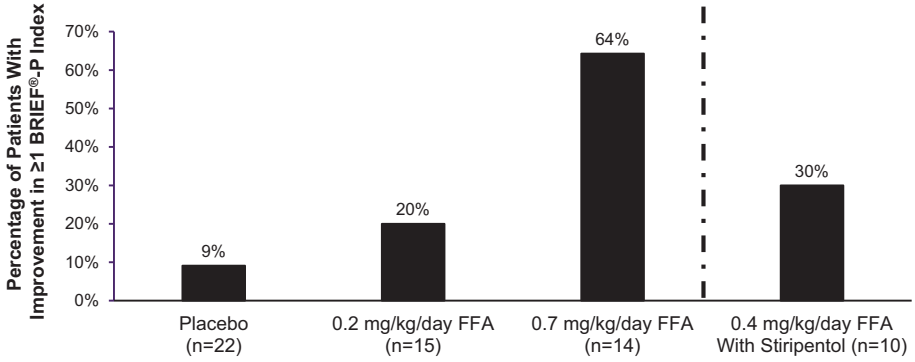

Fig. 1. Percentage of individual preschool children with DS showing reliable, clinically meaningful improvement (RCI ≥ 90% certainty) in at least one index in the BRIEF®-P (n = 17/61). Of these 17 patients, median percentage reduction in monthly convulsive seizure frequency was ≥ 50% in 10 patients (59%), including 6/9 in the 0.7 mg/kg/day FFA group, 2/3 patients in the 0.4 mg/kg/day (with stiripentol) group, 1/3 patients in the 0.2 mg/kg/day group, and 1/2 patients in the placebo group (see Table 6). Hashed line: FFA 0.4 mg/kg/day with stiripentol results in levels of systemic fenfluramine that are pharmacokinetically similar to FFA 0.7 mg/kg/day regimens without stiripentol due to known drug-drug interactions. BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version; FFA, fenfluramine.

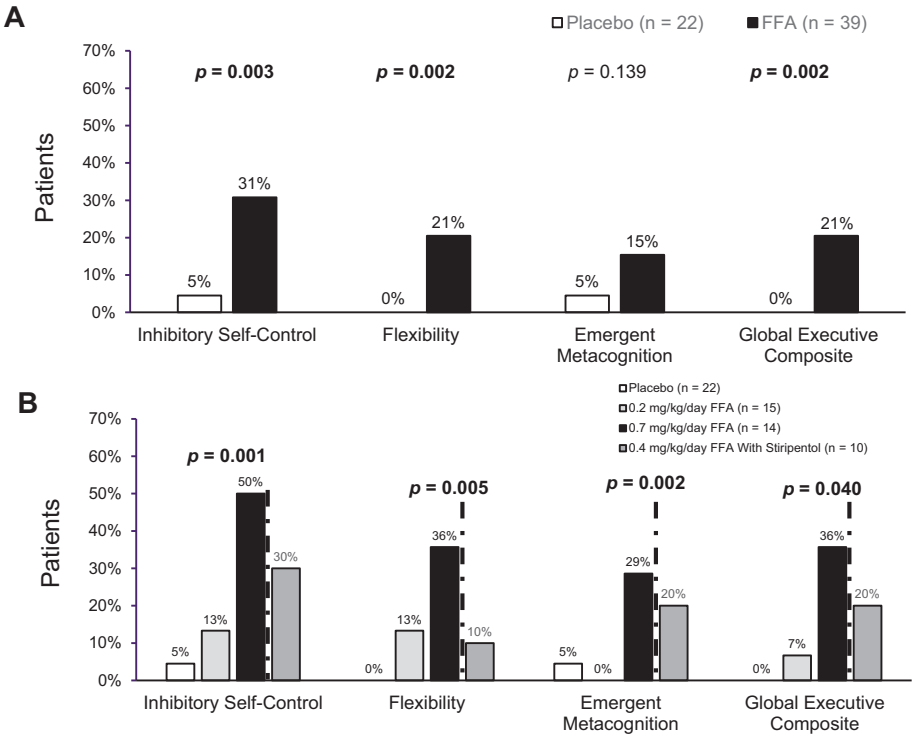

Fig. 2. Percentage of individual preschool children with DS showing reliable, clinically meaningful improvement (RCI ≥ 90% certainty) in BRIEF®-P indexes/composite T-scores for (A) placebo and FFA combined (0.2 mg/kg/day, 0.4 mg/kg/day [with stiripentol], and 0.7 mg/kg/day) treatment groups, or (B) the four individual treatment groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], and FFA 0.7 mg/kg/day) (N = 61). Hashed line: FFA 0.4 mg/kg/day with stiripentol results in levels of systemic fenfluramine that are pharmacokinetically similar to FFA 0.7 mg/kg/day regimens without stiripentol due to known drug-drug interactions. *p*-values are associations between placebo vs FFA combined (0.2 mg/kg/day, 0.4 mg/kg/day [with stiripentol], and 0.7 mg/kg/day) treatment groups and the likelihood of reliable, clinically meaningful improvement in BRIEF®-P indexes/composite T-scores (A), or between the four individual treatment groups (placebo, 0.2 mg/kg/day FFA, 0.4 mg/kg/day FFA [with stiripentol], or 0.7 mg/kg/day FFA) and the likelihood of reliable, clinically meaningful improvement in BRIEF®-P indexes/composite T-scores (B); calculated by Somers' *d*. Values in bold font met *a priori* thresholds for statistical significance ($p \leq 0.05$). BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version; FFA, fenfluramine; RCI, Reliable Change Index.

including 3/9 children (33%) in the FFA 0.7 mg/kg/day group (Table 4; footnote to Fig. 1).

3.3. Associations between treatment and everyday EF: Placebo vs FFA combined (0.2 mg/kg/day, 0.4 mg/kg/day [with stiripentol], and 0.7 mg/kg/day)

The effect of FFA treatment (combined treatment groups) was compared to placebo for each individual BRIEF®-P index/composite (Fig. 2**A**). There were positive associations between placebo vs FFA combined treatment groups and the likelihood of reliable, clinically meaningful improvement in ISCI (d = 0.262, p = 0.003), FI (d = 0.205, p = 0.002), and GEC (d = 0.205, p = 0.002), but not EMI (p = 0.139) (Fig. 2**A**; RCI ≥ 90% certainty). Treatment with FFA showed a significantly greater likelihood of reliable, clinically meaningful improvement than placebo in ISCI (31% vs 5%, V = 0.308, p = 0.022), FI (21% vs 0%, V = 0.292, p = 0.042), and GEC (21% vs 0%, V = 0.292, p = 0.042), but not in EMI (15% vs 5%, p = 0.405) (Table 5).

No associations were observed between the placebo vs FFA combined treatment groups and the likelihood of reliable, clinically meaningful worsening (RCI ≥ 80% certainty) for any of the BRIEF®-P indexes/composite T-scores ($p > 0.05$).

3.4. Associations between treatment and everyday EF: Four individual treatment groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], or FFA 0.7 mg/kg/day)

To determine whether the effects of FFA on each BRIEF®-P index/composite were dose-dependent, associations were evaluated between the four individual treatment groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], and FFA 0.7 mg/kg/day) (Fig. 2**B**). Overall, there were positive associations between the four individual treatment groups and the likelihood of clinically meaningful improvement in ISCI (d = 0.261, p = 0.001), FI (d = 0.187, p = 0.005), EMI (d = 0.144, p = 0.040), and GEC (d = 0.205, p = 0.002) (Fig. 2**B**; RCI ≥ 90% certainty). The

Table 5
Post-hoc Two-Sided Fisher's Exact Tests to Determine Whether the Likelihood of Reliable, Clinically Meaningful Improvement in FFA Combined (0.2 mg/kg/day, 0.4 mg/kg/day [with stiripentol], and 0.7 mg/kg/day) Treatment Groups and Placebo Differed Significantly From One Another at RCI ≥ 90% (N = 61).

Characteristic	Placebo (n = 22)
BRIEF®-P Indexes/ Composite	
Inhibitory Self-Control, *p*-values[a]	
FFA Combined vs:	**p = 0.022**
Flexibility, *p*-values[a]	
FFA Combined vs:	**p = 0.042**
Emergent Metacognition, *p*-values[a]	
FFA Combined vs:	NS
Global Executive Composite, *p*-values[a]	
FFA Combined vs:	**p = 0.042**

BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version; FFA, fenfluramine; NS, not significant ($p > 0.05$).
[a] Values in bold font met the *a priori* significance threshold ($p \leq 0.05$; post-hoc Fisher's Exact test).

FFA 0.7 mg/kg/day dose group showed a greater likelihood of reliable, clinically meaningful improvement than placebo in ISCI (50% vs 5%, $V = 0.533$, $p = 0.003$), FI (36% vs 0%, $V = 0.503$, $p = 0.005$), and GEC (36% vs 0%, $V = 0.503$, $p = 0.005$); the likelihood of clinically meaningful improvement over placebo did not meet the *a priori* significance threshold for EMI (29% vs 5%, $p = 0.064$) (Table 6). The FFA 0.7 mg/kg/day dose group also showed a greater likelihood of reliable, clinically meaningful improvement than the FFA 0.2 mg/kg/day group in ISCI (50% vs 13%, $V = 0.396$, $p = 0.050$) and EMI (29% vs 0%, $V = 0.414$, $p = 0.042$), but did not meet the *a priori* significance threshold for GEC (36% vs 7%, $p = 0.080$) (Table 6). The FFA 0.4 mg/kg/day (with stiripentol) group did not meet the *a priori* significance threshold for a greater likelihood of reliable, clinically meaningful improvement than placebo in ISCI (30% vs 5%, $p = 0.079$) or GEC (20% vs 0%, $p = 0.091$) (Table 6). Per the significance threshold ($p \leq 0.05$), there were no significant differences in proportions of children showing reliable, clinically meaningful improvement between the FFA 0.2 mg/kg/day group and placebo group, between the FFA 0.2 mg/kg/day and FFA 0.4 mg/kg/day (with stiripentol) treatment groups, or between the FFA 0.4 mg/kg/day (with stiripentol) and FFA 0.7 mg/kg/day treatment groups in any index/composite T-scores.

No associations between the four individual treatment groups and the likelihood of reliable, clinically meaningful worsening (RCI $\geq$ 80% certainty) were observed for any of the BRIEF®-P indexes/composite T-scores ($p > 0.05$).

Table 6
Post-hoc Two-Sided Fisher's Exact Tests to Determine Whether the Likelihood of Reliable, Clinically Meaningful Improvement in the Four Individual Treatment Groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], and FFA 0.7 mg/kg/day) Differed Significantly From One Another at RCI $\geq$ 90% (N = 61).

Characteristic	Placebo (n = 22)	FFA, 0.2 mg/kg/day (n = 15)
BRIEF®-P Indexes/ Composite		
Inhibitory Self-Control, *p*-values[a]		
0.7 mg/kg/day FFA (n = 14) vs:	***p* = 0.003**	***p* = 0.050**
0.4 mg/kg/day FFA with stiripentol (n = 10) vs:	$p = 0.079$	NS
Flexibility, *p*-values[a]		
0.7 mg/kg/day FFA (n = 14) vs:	***p* = 0.005**	NS
0.4 mg/kg/day FFA with stiripentol (n = 10) vs:	NS	NS
Emergent Metacognition, *p*-values[a]		
0.7 mg/kg/day FFA (n = 14) vs:	$p = 0.064$	***p* = 0.042**
0.4 mg/kg/day with stiripentol FFA (n = 10) vs:	NS	NS
Global Executive Composite, *p*-values[a]		
0.7 mg/kg/day FFA (n = 14) vs:	***p* = 0.005**	$p = 0.080$
0.4 mg/kg/day FFA with stiripentol (n = 10) vs:	$p = 0.091$	NS

BRIEF®-P, Behavior Rating Inventory of Executive Function®—Preschool Version; FFA, fenfluramine; NS, not significant ($p > 0.05$).

[a] Values in bold font met the *a priori* significance threshold ($p \leq 0.05$). Per significance threshold ($p \leq 0.05$), there were no differences in proportions of children showing reliable, clinically meaningful improvement between the 0.2 mg/kg/day FFA group and placebo group, between the 0.2 mg/kg/day FFA and 0.4 mg/kg/day FFA (with stiripentol) treatment groups, or between the 0.4 mg/kg/day FFA (with stiripentol) and 0.7 mg/kg/day FFA treatment groups in any index/composite T-score at RCI $\geq$ 90% certainty.

4. Discussion

This study is the first to demonstrate improvements in everyday EF in preschool-aged children with DS after a relatively short, 14- to 15-week, FFA treatment duration. We examined associations between treatment groups (placebo, FFA 0.2 mg/kg/day, FFA 0.4 mg/kg/day [with stiripentol], and FFA 0.7 mg/kg/day) and the likelihood of reliable, clinically meaningful improvement in everyday EF in young children with DS aged 2 to 4 years with high baseline rates of impairment in everyday EF. Overall, approximately one- fourth of children with DS treated with FFA experienced improvements in at least one aspect of everyday EF (regulation of behavior, emotion, and/or cognition). These improvements were dose-dependent and could not entirely be considered secondary to improved seizure control. These results are consistent with a prior report showing that seizure frequency was not significantly correlated with BRIEF®-P indexes in preschool-age children with epilepsy [43].

More children in the FFA 0.7 mg/kg/day group than the placebo group showed a greater likelihood of reliable, clinically meaningful improvement in (1) the ability to control impulses and emotional outbursts as measured by the ISCI, (2) the ability to adapt to change and regulate emotions as measured by the FI, and (3) overall everyday EF (self-regulation) as measured by the overarching GEC. In addition, more children receiving the FFA 0.7 mg/kg/day than the FFA 0.2 mg/kg/day dosage had improvements in working memory and planning/organizing as measured by the EMI. Maiman et al. (2017) also found that emergent metacognition was the most frequently elevated index in preschool children with epilepsy [43]. There were no associations among treatment groups with reliable, clinically meaningful worsening of everyday EF, suggesting that treatment with FFA did not adversely affect everyday EF in this patient population.

Neurodevelopmental delay with impairments in executive functioning is a major challenge for patients with DEEs and their caregivers [52,53]. During the preschool years, these impairments may place a child on a trajectory toward progressively worsening function later in life [54,55]. The preschool years also represent the early formative stages of everyday EF development [42,43,56]. The high frequency of baseline everyday EF impairment observed in our study is consistent with the developmental trajectories of patients with DS, where developmental delay becomes apparent between the ages of 2 to 4 years [57]. By adulthood, most patients with DS are too impaired to function independently and require lifelong care [53,58]. Although ASMs are an essential part of seizure reduction, they may also be associated with effects (positive or negative) on behavior, emotion, and cognition [59]. Therefore, the effect of ASMs represents a potentially modifiable factor in patients with developmental and epileptic encephalopathies [60]. Current consensus guidelines recommend early treatment to improve long-term clinical outcomes in patients with DS [61]. The improvements in everyday EF after FFA observed in our study may have important implications for short- and longer-term developmental trajectories of everyday EF in children with DS. In neurotypical individuals, the ability to regulate behavior, emotion, and attentional control begins in infancy [56] and develops rapidly during the preschool years [56,62–65]. Early acquisition of these fundamental EFs is a precursor to the later development of the ability to plan, organize, and self-monitor goal-oriented, problem-solving behavior [63,66]. Treatments that have a beneficial impact on early EF have the potential to facilitate the later development of all aspects of self-regulation. The results of our study suggest that when added to the patient's baseline standard-of-care regimen, FFA was not associated with clinical worsening of everyday EF. Rather, FFA may be effective in some patients at an early age in improving their ability to regulate behavior, emotions, and/or cognition. Long-term follow-up studies are needed to test whether early intervention with FFA confers long-term clinical benefit through childhood and adolescence.

Our results are consistent with a recent report of clinical benefit after FFA treatment on both seizures and nonseizure quality-of-life outcomes, including ratings of attention and memory in patients with DS aged 2 to 33 years [67]. The majority of caregivers also reported improvements in their child's cognition, academic performance, and alertness after FFA treatment, in addition to seizure-related improvements. A prior study in preschool-aged children with epilepsy showed that the age of seizure onset, seizure frequency, and the number of antiseizure medications were not significantly correlated with BRIEF®-P indexes [43]. However, these authors note that BRIEF®-P scores may vary across epilepsy subgroups. To date, no study has examined change in everyday EF after FFA as the primary study endpoint in preschool-aged children with DS.

Associations between seizures and nonseizure outcomes were not evaluated in these analyses. Although this study provides some clinical evidence that FFA confers clinical benefit in nonseizure outcomes, the question of whether these improvements are a direct effect of FFA or secondary to improved seizure control is an area of active investigation. Nonseizure comorbidities in DS arise both as an indirect effect of prolonged seizure activity in neurodevelopment and as direct effects of SCN1A haploinsufficiency in different brain regions (interrelated factors) [68,69]. In a previous study in children and young adults with DS treated with FFA for 1 year, we reported that a greater percentage of children had improvements in EF if they had $\geq$ 50% reduction in seizure frequency than those with a < 50% reduction [15]. These data are consistent with the current study, where more patients with $\geq$ 50% reduction in seizure frequency also had improvements in at least one BRIEF®-P index.

However, the results of our study also suggest that FFA may have direct effects on everyday EF beyond improvements that are secondary to seizure reduction. These data are hypothesis-generating, and support conducting larger studies that are specifically powered to assess everyday EF outcomes as a primary endpoint. More recent reports published in abstract form provide further support for the direct effects of FFA in improving everyday EF in children with DS or LGS treated with FFA over relatively short treatment periods (14–15 weeks), and that these improvements are not solely the effects of change in seizure frequency [21–26]. Investigations examining a potential direct effect of FFA on executive functions in healthy adult volunteers (18–22 years) are also ongoing (NCT05026398).

The pharmacology of FFA also suggests there may be direct effects on nonseizure outcomes, including everyday EF, in addition to mechanisms secondary to seizure control [31–34,70,71]. To date, FFA is the only medication with dual 5-HT and σ1R pharmacology that is approved for the treatment of DS or LGS [33,35,72–76]. Apart from pilot findings [77], clinical studies have not investigated the role(s) of this unique pharmacology in healthy volunteers or patients. Preclinical research supports a role for 5-HT receptors in aspects of cognition and executive functions specifically, with implications for the regulation of behavioral inhibition, flexibility, and attention [78–80]. Recent clinical studies in healthy volunteers support a pro-cognitive role for pharmacological agonists at 5-HT_4 receptors [34], suggesting that activity at 5-HT_4 receptors may be one potential pharmacological mechanism for a direct effect of FFA on everyday EF. Preclinical data support a role for FFA activity at 5-HT_4 receptors [71], but further studies are needed to confirm this hypothesis.

Similarly, selective σ1R drug candidates are being developed based on recent preclinical data demonstrating σ1R-mediated effects on learning, cognition, emotion, and other neurological functions [81]. Recent preclinical studies support distinct mechanisms of action for FFA's ability to improve seizure control and impact nonseizure outcomes, including behavior, learning, and memory [32,33,35,82].

Our study is consistent with earlier findings that support no reliable, clinically meaningful worsening of everyday EF after treatment with FFA [20]. In clinical practice, managing the adverse effects of ASMs is an important consideration in conjunction with managing seizures and neurodevelopmental outcomes, including the effects of multi-ASM regimens on a child's ability to regulate their everyday behavior, emotions, and cognition [18,19,57,59]. Our results are also consistent with prior reports that support a reliable, clinically meaningful improvement in everyday EF [20]. Taken together, these data suggest that treatment with FFA initiated in young children may confer benefits in everyday EF with long-term developmental impact [27,59,60]. Further studies examining change in everyday EF after FFA treatment when added to a baseline standard-of-care regimen in preschool-aged children with DS are needed. The effect of FFA treatment with different concomitant medication combinations on everyday EF must also be considered [59].

This study has several notable strengths. First, the RCT design allowed for analyses of associations between treatment groups and the likelihood of reliable, clinically meaningful change in an unbiased manner. It reduces selection bias that is not afforded in the OLE of this study, where the patients, parents/caregivers, and investigators were not aware of whether the child was receiving placebo or FFA. Second, our study has a sample size that is relatively large and well-characterized in relation to previously published cohorts evaluating EF in patients with treatment-resistant epilepsies [18,19], although it should be noted that subdividing the sample into treatment groups resulted in smaller sample sizes per treatment group (unavoidable in rare conditions such as DS). Third, this study measured everyday EF with the BRIEF®-P parent form, a standardized measure with desirable psychometrics that captures views of a preschool child's EFs or self-regulation in his or her everyday environment [42]. Assessment of EFs solely with performance tests can yield an incomplete picture of EF with limited 'ecological' validity [83,84]. Performance-based tests tap limited components of the EF system over a short time frame and not the integrated application of multiple EFs through specific cognitive domains (e.g., attention, memory) in the affectively charged, socially important, and culturally facilitated everyday world [85,86]. EF assessment with young children is challenging, given the variability of behavior, motor, and verbal development in this age range. The use of the BRIEF®-P parent form in this study compensates for several of these challenges in the traditional test-based assessment of EF. This observer-reported outcome (ObsRO) measure approach is easily applied in global trials of patients who cannot report for themselves (e.g., infants, individuals who are cognitively impaired, and vulnerable and special populations). The BRIEF®-P parent form is supported by large neurotypical normative samples, making it particularly useful for evaluating reliable, clinically meaningful change in everyday EF after investigational drug treatment. The BRIEF®-P is predictive of real-world functioning and has strong ecological validity [83,87,88]. Improvement in a parent/caregiver's perception of their child's everyday EF problems may result in reduced caregiver burden.

Fourth, the focus of our post-hoc exploratory ("hypothesis-gen erating") analyses was to examine reliable, clinically meaningful changes as defined by RCIs in BRIEF®-P indexes/composite T-scores that are relative to a neurotypical population. The RCI method is intended to take into account practice effects and other sources of variation when determining a change in performance over time. This approach shows the proportion of preschoolers who change (improvement or worsening) beyond what might occur by chance or error. In other words, is an individual's change

reliable (i.e., is the magnitude of the observed change more than can be explained by errors of measurement?) and has the individual made a big enough change during treatment for this to be regarded as important (i.e., is the change clinically significant)? In this way, the use of RCIs is one indication of effect size. Such individual responsiveness is important to future efforts to develop and refine treatments. To our knowledge, this is the first phase III study in young children with DS to apply RCIs in an experimental design. Our findings may be relevant to a range of scientific disciplines, including medicine and psychology.

This study has some important limitations. First, the treatment duration of the RCT was relatively short for observing reliable, clinically meaningful changes in everyday EF. Treatment durations greater than 1 year may reveal more stable reliable, clinically meaningful changes in outcomes. Additional analyses are underway to evaluate changes over longer time intervals using OLE data from the DS and LGS phase III programs. Second, our study was neither designed to evaluate everyday EF as a primary efficacy endpoint nor was it specifically powered to detect a statistically significant difference in everyday EF. Third, most clinical studies powered for everyday EF endpoints consider an RCI $\geq$ 80% certainty to be a reliable, clinically meaningful change (improvement or worsening) in T-scores over time [47,48]. As a post-hoc exploratory analysis, however, we opted to use a more stringent and cautious level (RCI $\geq$ 90%; see also supplemental analysis at RCI $\geq$ 95% certainty) for reliable, clinically meaningful improvement. As a result, we may have reported fewer cases of reliable, clinically meaningful improvement. We also did not statistically correct for multiple comparisons. Fourth, we consider the results of this study as hypothesis-generating in terms of evaluating a direct effect of FFA on aspects of everyday EF, specifically everyday regulation of behavior, emotion, and cognition. Whether the improvements in everyday EF after FFA treatment are direct effects of FFA and/or secondary to improved seizure control is difficult to determine experimentally. Several interrelated factors contribute to adverse effects in patients with epilepsy: seizures and subclinical epileptiform activity, underlying etiology and developmental and psychological comorbidities, and the known cognitive deficits of some ASMs [59,60]. Future studies may more directly address questions of everyday EF in preschool children with DS.

Fifth, ASMs have the potential to contribute to impairments in behavior, emotions, and cognition [59,89]. Although one of the inclusion criteria for entry into the RCT was the expectation that concomitant ASMs would remain stable for the trial duration, it should be noted that clinical improvement during FFA treatment in real-world dosing scenarios may prompt reduction in the overall medication burden [74], which could also contribute, at least in part, to improvements in everyday EF. Stiripentol inhibits FFA metabolism, thereby requiring a downward dosing adjustment to attain systemic FFA concentrations that are pharmacokinetically similar to stiripentol-free regimens [39,41,90,91]. The implications of the apparent differences we observed on everyday EF among the pharmacokinetically similar FFA 0.7 mg/kg/day and FFA 0.4 mg/kg/day (with stiripentol) remain to be evaluated. In addition, stiripentol-clobazam combination regimens frequently used in patients with DS result in elevated systemic levels of clobazam, a drug known to be sedating at higher doses [92,93]. Finally, the debate continues on how best to assess EF [94,95]. While the use of ObsRO assessments of everyday EF conveys benefits, there are also limitations inherent in using rating scales [59,96–98].

With the completion of a third pivotal study of FFA for DS [99], evaluating everyday EF in a larger patient pool over longer treatment durations is now possible. At the time of the last analysis, 330 patients with DS in the OLE had a median treatment duration of 631 days (ranging up to 1086 days, or approximately 3 years) [100], thereby enabling data analysis at longer time points, albeit without the strength of blinding and placebo control. Comparing DEEs where FFA has a lower magnitude of effect on seizure burden will also facilitate in differentiating between the effects of FFA on everyday EF independent of seizure control. Comparing improvements over time relative to when FFA is started—early in neurodevelopment (<5 years) versus later in disease progression (5–18 years, >18 years)—will allow further assessment of the disease-modifying potential of FFA to alter the natural history of DS and other DEEs. Evaluating BRIEF®-P data in the context of general development, adaptive behavior, and quality of life may be important in understanding the broader impact of self-regulation. Finally, the patient and rater's mood should be considered when interpreting rating scales, as they may influence scores.

5. Conclusions

In this cohort of preschool-aged children with DS with high baseline everyday EF impairment, FFA treatment for 14 to 15 weeks was associated with reliable, clinically meaningful improvements in inhibitory self-control, flexibility, emergent metacognition, and overall everyday EF (self-regulation). Responses were dose-dependent and improvement in everyday EF did not appear to be entirely due to seizure control. There were no indications of reliable, clinically meaningful worsening in everyday EF with FFA treatment. Early intervention with treatments that can improve everyday EF during these critical formative years in neurodevelopment has the potential to improve the natural history of DS. Further research is warranted to understand the long-term impact of treatment with FFA in preschool-aged children with DS, including the potential for the longer-term development of cognitive regulation.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Dr. Bishop** is Principal Consultant for Global Pharma Consultancy, LLC, which has received consultancy fees from Zogenix for research support; **Dr. Isquith** and **Dr. Gioia** are Associate Consultants for Global Pharma Consultancy, LLC, which has received consultancy fees from Zogenix for research support, and have received royalties from Psychological Assessment Resources (PAR, Inc.) for sale of the BRIEF® instruments; **Dr. Knupp** received research grants during the conduct of the study from Zogenix and the Pediatric Epilepsy Research Foundation, and outside the submitted work received research grants from the Colorado Department of Public Health and West Therapeutics and was a DSMB member for Greenwich Pharmaceuticals; **Dr. Scheffer** received compensation from Zogenix during the conduct of the study; personal fees from GlaxoSmithKline, Eisai, BioMarin, Nutricia, and Xenon Pharmaceuticals outside the submitted work; research funding from the National Health and Medical Research Council, Health Research Council of New Zealand, and National Institutes of Health; personal fees and other compensation from UCB; and other compensation with Zynerba Pharmaceuticals, GW Pharmaceuticals, Ovid Therapeutics, Marinus, and Ultragenyx; **Dr. Nabbout** received research support from Eisai, GW Pharma, UCB, and Zogenix; served as a consultant/advisor for Eisai, Biogen, GW Pharma, Novartis, Shire, and Zogenix; and served in a speaker role for Advicenne, Eisai, BioMarin, GW Pharma, Novartis, and Zogenix; **Dr. Specchio** has received consulting fees from Zogenix and support from LivaNova, BioMarin; she has served as a paid consultant for LivaNova; **Dr. Sullivan** received research grants from Zogenix (with travel support), Stoke, Marinus, and Biopharm; has served as a consultant/advisor for the Dravet

Syndrome Foundation, Epygenix, Encoded, GW Pharma, Asceneuron, Longboard Pharmaceuticals, Knopp Biosciences, and Neurocrine; as a reviewer for the Epilepsy Study Consortium; and has stock options in Epygenix; **Dr. Auvin** has received personal fees from Arvelle, Biocodex, GW Pharma, and Xenon; personal fees and nonfinancial support from Biomarin, GW Pharma, and Nutricia; personal fees/grants from Eisai and UCB Pharma for work as an investigator; and research support from Zogenix; **Dr. Cross** received grants from Zogenix, Marinus, GW Pharma, Vitaflo, the National Institute of Health Research (NIHR), EPSRC, GOSH Charity, ERUK, the Waterloo Foundation, and the Great Ormond Street Hospital Biomedical Research Centre; she has been a consultant/advisor for Zogenix and GW Pharma, for which remuneration was made to the department outside of the submitted work; chair of the Medical Board for DravetUK, Hope for Hypothalamic Hamartoma, and Matthew's Friends; supported by the NIHR Biomedical Research Centre at Great Ormond Street Hospital; endowed chair at UCL Great Ormond Street Institute of Child Health; **Dr. Guerrini** received research grants from Zogenix during the conduct of the study and received personal fees as a speaker or consultant from Zogenix outside the submitted work; he has served as an investigator for studies with Biocodex, UCB, Angelini, and Eisai Inc, and as a speaker/advisory board member for Biocodex, Novartis, Biomarin, and GW Pharma outside the submitted work; **Dr. Gammaitoni, Dr. Galer, and Dr. Farfel** were employees of and had ownership interest in Zogenix at the time of the study.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108994.

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