Improved everyday executive functioning following profound reduction in seizure frequency with fenfluramine: Analysis from a phase 3 long-term extension study in children/young adults with Dravet syndrome

Kim I. Bishop, Peter K. Isquith, Gerard A. Gioia, Arnold R. Gammaitoni, Gail Farfel, Bradley S. Galer, Rima Nabbout, Elaine C. Wirrell, Tilman PNST, Joseph Sullivan

Objective: Individuals with Dravet syndrome (DS) experience frequent pharmacoresistant seizures beginning in infancy. Most exhibit poor neurodevelopmental outcomes including motor function difficulties, behavior problems, and cognitive impairment. Cognitive deficits in children with DS have been associated with seizure frequency and antiseizure medication (ASM) use.

Recent research in children and young adults with DS has begun to examine the role of executive functions (EFs), as these include higher-order cognitive functions and may mediate the relationship between risk factors and cognitive impairment. Current conceptualizations, however, of EFs involve the broader self-regulation of cognitive, behavioral, and emotional domains. We explored relationships between reduction in convulsive seizure frequency and everyday EFs in a subset of children and young adults with DS treated with adjunctive fenfluramine for 1 year.

Methods: This is a post-hoc analysis of data from children and young adults with Dravet syndrome aged 5-18 years who participated in a phase 3 randomized, placebo-controlled clinical trial (core study) followed by completion of at least 1 year of fenfluramine treatment in an open-label extension (OLE) study. Eligible children and young adults started the OLE study at 0.2 mg/kg/day fenfluramine and were titrated to optimal seizure control and tolerability (maximum daily dose: 24 mg/day). Parents/caregivers documented convulsive seizure frequency per 28 days (i.e., monthly convulsive seizure frequency [MCSF]) by electronic diary. A parent/caregiver for each child also completed the Behavior Rating Inventory of Executive Function (BRIEF) parent form, a questionnaire capturing parents’/caregivers’ perceptions of everyday EF that was included as a safety measure to assess treatment-related adverse effects on EF during the trial. Ratings on BRIEF were mapped to the current edition, the BRIEF parent form, and were used to calculate T-scores for the Behavior Regulation Index (BRI), Emotion Regulation Index (ERI), Cognitive Regulation Index (CRI), and Global Executive Composite (GEC). Change in BRIEF T-scores from baseline to Year 1 of the OLE study was calculated. Spearman’s rho correlation coefficients assessed associations between change in BRIEF indexes/composite T-scores and percentage change in MCSF. Children and young adults were divided into 2 groups based on percentage of MCSF reduction achieved from pre-randomization baseline to Year 1 of the OLE study: <50% and ≥50% MCSF reduction. Changes in the distribution of BRIEF indexes/composite T-scores were compared between MCSF reduction groups using Mann-Whitney U tests. The proportions of children and young adults in these groups who showed clinically meaningful improvement in everyday EF, defined as

Keywords:
- Behavior Rating Inventory of Executive Function, 2nd edition (BRIEF)
- Dravet syndrome
- Fenfluramine
- Seizure frequency
1. Introduction

Dravet syndrome (DS) is a rare, lifelong developmental and epileptic encephalopathy with frequent and/or prolonged drug-resistant seizures that typically begin in the first year of life in developmentally normal infants [1–6]. Most cases of DS (approximately 80%) carry de novo mutations of SCN1A, the gene encoding the α1 subunit of the voltage-gated sodium channel [7–11]. Children with DS experience early-onset developmental delays across cognitive, adaptive, motor, and behavioral domains [1,3,12,13]. The degree of intellectual disability varies widely, from mild to severe [14–16], with most people with DS requiring lifelong care due to limitations in their ability to conduct normal activities of daily living [1,6,17–23].

The majority of research on neurodevelopmental outcomes in DS has focused on intellectual functioning and adaptive behavior deficits [14]. More recent research in very small samples of children with DS has found deficits in executive function (EF) [13,24]. Executive function has long been viewed as encompassing a variety of interrelated higher order cognitive abilities that are responsible for guiding, directing, and managing specific domains including memory, attention, language, etc. [25]. These include initiating, inhibiting, planning, and organizing, particularly during active novel problem-solving [26]. Current conceptualizations of EF include regulation of behavior and emotion in addition to traditional cognitive regulation models [26]. Executive dysfunction can interfere with a child’s daily life in many ways, including the ability to function independently at home, to attend school, and to develop and maintain appropriate social relationships [27]. Children with epilepsy may be at risk of developing EF deficits that may vary in presentation depending on epilepsy type and seizure severity [28].

In addition to frequent seizures in children and young adults with DS that may be associated with deficits in cognition, treatment with antiseizure medications (ASMs), which are often prescribed to reduce seizures, may further jeopardize cognition [22,29–31], possibly mediated, at least in part, by their effects on EF [32]. Individuals with DS almost always require polytherapy [33], which significantly increases the likelihood of adverse cognitive drug effects [30,32,34,35]. Children and young adults with DS represent a particularly vulnerable population because multi-ASM combinations can have negative additive effects on cognition [29,31], especially if seizures are poorly controlled, during their most developmentally sensitive time period [22,23]. To our knowledge, no studies have evaluated the long-term impact of ASMs on EF in children and young adults with DS.

Adjunctive fenfluramine demonstrated a high magnitude of reduction in convulsive seizure frequency in children and young adults with DS in a recent phase 3 randomized, placebo-controlled clinical trial (core study, Study 1; NCT02682927/NCT02826863) [36]. There was no evidence that everyday EF, as measured by parent/caregiver ratings over the treatment period, worsened in association with fenfluramine treatment. Instead, some aspects of everyday EF improved over the relatively short treatment duration of 14 weeks [36,37]. The objective of the current analysis was to fully explore the relationship between long-term fenfluramine treatment and everyday EF in an open-label extension study (OLE).

The aims of this exploratory analysis were twofold: (1) to evaluate the overall relationship between changes in seizure frequency and changes in everyday EF in children and young adults with DS receiving long-term (1 year) add-on fenfluramine as part of an OLE, and (2) to compare the proportions of children and young adults with <50% and ≥50% MCSF reduction who experienced clinically meaningful changes in everyday EF. We hypothesized that long-term treatment with fenfluramine would result in improvement in everyday EF, and that improvements in EF would be greater among children and young adults with greater percentages of MCSF reduction.

2. Materials and methods

2.1. Data

Data for this post-hoc analysis were collected for children and young adults with DS who transitioned from a 14-week phase 3 randomized, placebo-controlled clinical trial (RCT, core study; Study 1; NCT02682927/NCT02826863) [36] to an OLE (Study
1503; NCT02823145) and had completed at least 1 year of add-on fenfluramine treatment. Eligible children and young adults who transitioned into the OLE began treatment at 0.2 mg/kg/day fenfluramine, which was titrated to effect (maximum: 26 mg/day fenfluramine). Reduction in monthly convulsive seizure frequency (MCSF, per 28 days) was calculated using the percentage change in seizure frequency from baseline in the core study to Year 1 of the OLE. Children and young adults were divided into 2 groups based on their level of MCSF reduction from baseline in the core study to Year 1 of the OLE: <50% MCSF reduction (sub-threshold clinical response for the primary endpoint) and ≥50% (widely accepted as a clinically meaningful level of response in terms of seizure frequency reduction). A supplemental analysis examined MCSF reduction from baseline in the core study to Year 1 of the OLE in groups with <25% MCSF reduction (minimal clinical response) and ≥75% MCSF reduction (a profound level of response).

2.2. Executive function endpoints

The BRIEF² parent form for children and young adults 5–18 years of age [38] or the BRIEF²-Preschool Version (BRIEF²-P) for preschool children 2–5 years of age [36] was completed in the core study to assess potential adverse effects of fenfluramine on everyday executive functioning [22]. Per the core study and OLE study protocols, BRIEF² or BRIEF²-P was completed by parents/caregivers of enrolled children and young adults at pre-randomization baseline and periodically throughout both the core study and the OLE, as described previously [36,39]. In the posthoc analysis, parent/caregiver responses at pre-randomization baseline and at OLE Year 1 on BRIEF² were mapped to the updated 63-item edition, BRIEF². The new edition incorporates a new normative sample and statistics to support interpretation (e.g., reliable change indexes) [26]. As BRIEF² has been validated only for children and young adults 5–18 years of age, children 2–4 years of age who were assessed with BRIEF²-P were excluded from this post-hoc analysis.

For each of the 63 items on BRIEF², parents/caregivers rate how often their child has problems with each characteristic, such as impulsivity, emotional outbursts, and difficulty focusing attention, planning, or organizing, using a 3-point rating scale (1 = never a problem, 2 = sometimes a problem, 3 = often a problem). Responses to items reflect nine non-overlapping scales, which in turn comprise 3 indexes. BRIEF² indexes include the Behavior Regulation Index (BRI), composed of the Inhibit and Self-Monitor scales, which reference a child’s ability to regulate and monitor behavior effectively, including inhibiting impulses; the Emotion Regulation Index (ERI), composed of the Shift and Emotional Control scales, which reference a child’s ability to regulate emotional responses, including responding to changing situations; and the Cognitive Regulation Index (CRI), composed of the Initiate, Working Memory, Plan/Organize, Task Monitor, and Organization Materials scales, which reference a child’s ability to regulate thinking and attention and to solve problems effectively. A Global Executive Composite (GEC) represents an overall EF summary score (Table 1). If there are significant differences in any of the indexes, then the GEC is not interpreted because it is likely to obscure important differences among BRI, ERI, and CRI T-scores. Ratings are expressed as T-scores with a mean of 50 (±10) relative to a normative population of 1,400 neurotypical individuals matched to US population parameters for age, gender, parent education level, race/ethnicity, and geographic region [26,37]. In clinical settings, a T-score ≥65 (≥1.5 standard deviations [SDs] from the mean, or approximately the 93rd percentile) is generally accepted as the threshold for potential difficulties on behavior rating scales [26,40,41]. BRIEF² T-scores range from approximately 36 to >99, with lower scores reflecting better EF [26].

2.3. Study ethics

The original RCT and OLE studies were conducted in accordance with ethics and principles of the Declaration of Helsinki and Good Clinical Practice per the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline. The protocol was approved

| Table 1 | Description of BRIEF² Parent Form indexes/composite and reliable change indexes (RCIs) by confidence interval (±T-score points),⁴ [26,38] |
|---|---|---|---|---|
| BRIEF² indexes/composite | Description | Real-world examples | RCI >80% | RCI >95% |
| Behavior Regulation Index (BRI) | Captures the child’s ability to regulate and monitor behavior effectively including response inhibition/ impulse control | Children with elevated scores on the BRI are typically described as impulsive and as socially intrusive. Examples include controlling impulses, stopping behavior when needed, and keeping track of how one’s behavior or comments affects others. | 6–7 points | 9–11 points |
| Emotion Regulation 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 | Children with elevated scores on the ERI are often described as inflexible or not adaptable to new things or people or situations and/or as having strong emotional reactions or outbursts frequently. Examples include regulating or modulating emotional reactions and moving flexibly or adaptively to new situations or activities | 6–7 points | 9–11 points |
| Cognitive Regulation Index (CRI) | Reflects the ability to initiate, sustain, plan, and organize cognitive processes while holding goals in active working memory | Children with elevated scores on the CRI are often described as inattentive, distractible, and disorganized. They require prompts to get started on things and do not notice their mistakes. Examples include getting started on tasks or activities, remaining attentive or focused, holding information in active memory, planning and organizing activities or work, and monitoring success in achieving a goal | 5 points | 8–9 points |
| Global Executive Composite (GEC) | An overarching summary score that incorporates all BRIEF² items | Children with elevated scores on the GEC are typically described as globally dysregulated. The GEC is typically interpreted only when there are no meaningful patterns of scores on the BRI, ERI, or CRI | 5–6 points | 8–10 points |

⁴For this analysis, the lower point value in each range was used as the threshold. N/A, not applicable.

If there are significant differences in the indexes, then GEC is not calculated because this could obscure results and increase the number of comparisons.

Reproduced by special permission of the Publisher, Psychological Assessment Resources, Inc. (PAR), 16204 North Florida Avenue, Lutz, Florida 33549, from the Behavior Rating Inventory of Executive Function, Second Edition Professional Manual by Gerard A. Gioia, PhD, Peter K. Isquith, PhD, Steven C. Guy, PhD, and Lauren Kenworthy, PhD, Copyright 1996, 1998, 2000, 2001, 2003, 2004, 2015 by PAR, Table G.1, page 264. Further reproduction is prohibited without permission from PAR.
by the applicable competent regulatory authorities and independent ethics committee (IEC)/institutional review board (IRB) at each participating institution before study initiation. All children and young adults or their legal representatives provided signed informed consent before trial enrollment.

2.4. Statistical analysis

All statistics were calculated with SPSS Statistics Version 26. Descriptive statistics (n, mean, median, SD, range) were used to describe children and young adult demographics, including age, gender, MCSF, ASMs, and BRIEF®2 T-scores. A t-test was used to test for differences in ages between the 2 MCSF groups (<50% vs. ≥50%). Differences in gender among the 2 MCSF groups were then assessed by a chi-square test.

Nonparametric correlations using Spearman’s rho were used to measure the strength of association (p ≤ 0.05) between percentage change in MCF and BRIEF®2 indexes/composite T-score from baseline to OLE Year 1. Differences in BRIEF®2 indexes/composite T-score distributions between <50% and ≥50% MCSF reduction groups were assessed via Mann–Whitney U tests (p ≤ 0.05).

To determine if the degree of any change in scores, either improving or worsening, is clinically meaningful, we relied on Reliable Change Index (RCI) scores for BRI, ERI, CRI, and GEC as reported in the BRIEF®2 manual [26]. RCIs permit evaluation of statistically unexpected changes in outcome scores following treatment interventions beyond test-related error and practice effects. These RCI values take into account the standard error of measurement (SEM) at each testing time and its respective standard deviation and are used to establish confidence intervals at different levels of certainty [42]. With a rating scale such as BRIEF®2, which measures everyday executive functioning of the child or young adult, these statistically unexpected changes in outcome scores beyond test-related error and practice effects are viewed as having clinical significance in the life of the child or young adult and, therefore, as clinically meaningful.

A stringent RCI value ≥95% certainty was used to evaluate any potential improvement in children’s and young adults’ everyday EF associated with MCSF reduction. Clinically meaningful worsening was defined as RCI values ≥80% certainty. This RCI value was chosen to be more sensitive to any differences between groups with respect to worsening. Associations between MCSF reduction groups (<50% and ≥50%) and clinically meaningful improvement (RCI values <95% and ≥95%) in BRIEF®2 T-scores were evaluated using cross-tabulation. Somers’ D (p ≤ 0.05) was chosen as the statistic to test for associations between the two ordinal variables.

A post-hoc analysis using the same statistical methods was conducted to evaluate individual BRIEF®2 scales if there was a significant meaningful improvement in index scores.

A supplemental analysis compared change in EF in patients who demonstrated <25% and ≥75% MCSF reduction from baseline in the core study to Year 1 of the OLE. Proportions of patients who achieved clinically meaningful improvement or worsening in BRIEF®2 T-scores were determined at RCI values ≥95% and ≥80% certainty levels, respectively, but were not evaluated statistically due to the small number of patients in the <25% MCSF reduction group.

Cross-tabulation and Somers’ D test (p ≤ 0.05) were used to evaluate any potential differences between groups in clinically meaningful worsening of children’s and young adults’ everyday EF associated with MCSF reduction. RCI cutoff values for ≥95% and ≥80% certainty for the BRIEF®2 indexes/composite are shown in Table 1.

2.5. Data sharing

Zogenix, Inc., currently does not share individual-level patient data.

3. Results

3.1. Demographics and baseline characteristics

Of the 119 children and young adults included in the Study 1 RCT analysis cohort, 58 children and young adults constituted the analysis population for this study. The mean (±SD) age of the analyzed sample was 11 ± 4 years (range: 5–18 years). The analysis population completed at least 1 year of fenfluramine treatment in the OLE and had available data for both baseline in the core study and OLE Year 1 BRIEF®2. Table 2 shows core study baseline characteristics for the study sample. Mean age for the 2 groups was similar. Percentages of males and females were comparable in both groups.

### Table 2

| Characteristic | <50% MCSF reduction | ≥50% MCSF reduction | Overall |
|---------------|---------------------|---------------------|---------|
| n (%)         | 13 (22)             | 45 (78)             | 58 (100)|
| Age, years (mean ± SD, range) | 10 ± 3 (6–18) | 10 ± 3 (5–18) | 11 ± 4 (5–18) |
| Sex, n (%)    | Male 7 (54)         | Female 6 (46)       | 34 (59) |
| Concomitant ASMs, n (%) | 8 (62) | 21 (47) | 29 (50) |
| Valproate (all forms) | 4 (31) | 20 (44) | 24 (41) |
| Clobazam      | 8 (62)              | 21 (47)             | 29 (50) |
| Topiramate    | 4 (31)              | 9 (20)              | 13 (22) |
| Levetiracetam | 3 (23)              | 4 (9)               | 7 (12)  |
| MCSF at pre-randomization baseline | 11 (3–78) | 27 (5–624) | 26 (3–624) |
| Median        | 22 (25)             | 52 (93)             | 45 (84) |
| MCSF % change from pre-randomization baseline to OLE Year 1 | -21 | -85 | -75 |
| Median        | -48 to 61           | -100 to -51         | -100 to 61 |
| Mean (SD)     | 0.544 (0.090)       | 0.478 (0.139)       | 0.493 (0.132) |
| Median (range)| 0.570 (0.380–0.657) | 0.475 (0.173–0.665) | 0.497 (0.173–0.665) |

### Notes

*Percentages are calculated based on the totals in each group (i.e., n = 13 in the <50% MCSF reduction group; n = 45 in the ≥50% MCSF reduction group; n = 58 in the Overall group).

ASM, antiseizure medication; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency (per 28 days); OLE, open-label extension; SD, standard deviation.
The most common concomitant ASMs were clobazam (n = 29; 50%), valproate (n = 24; 41%), and topiramate (n = 13; 22%) (Table 2), with a mean of ~2 to 3 ASMs per patient [36]. At the time of analysis, all children and young adults had been treated with fenfluramine for at least 1 year at a median dose of 0.5 mg/kg/day for both groups (Table 2).

Among MCSF reduction groups at baseline in the core study, there were no statistically significant differences in median T-scores for any of the BRIEF®2 indexes nor for the composite score (Table 3). At pre-randomization baseline, parents'/caregivers’ responses corresponded to a wide range of scores on BRIEF®2, from a low of T = 37 to a high of T = 90 (Table 3). This range begins just over 1 SD below the normative mean T-score of 50 (SD = 10), indicating fewer problems in executive functioning, and extends up to 4 SDs above the normative mean T-score, indicating greater problems in executive functioning. Fifty-three percent (53%) of children and young adults had clinically elevated scores (T ≥ 65) on the BRI, 43% on the ERI, 40% on the CRI, and 59% on the GEC at baseline in the core study.

### 3.2. Effects of fenfluramine treatment on MCSF from baseline in the core study to OLE Year 1

After 1 year of fenfluramine treatment in the OLE, 78% (n = 45) of total patients achieved ≥50% reduction in MCSF, with 50% (n = 29) of total patients achieving ≥75% reduction in MCSF (Table 3). From pre-randomization baseline to OLE Year 1, the overall median reduction in MCSF was 21% in the <50% MCSF reduction group (range: 48% reduction to 61% increase) and 85% in the ≥50% MCSF reduction group (range: 51–100% reduction) (Table 3).

### 3.3. Overall correlations between change in MCSF and change in BRIEF®2 indexes/composite from baseline in the core study to OLE Year 1 overall

There was a statistically significant correlation between reduction in MCSF and improvement (negative change in T-score) on the ERI (r = 0.343; p = 0.008), but the relationship was not significant for BRI (r = 0.082), CRI (r = 0.121), and GEC (r = 0.217) (p > 0.05) (Fig. 1). Fig. 1 shows scatterplots with a linear fit line of percentage change in seizure frequency by change in BRIEF®2 indexes/composite from baseline in the core study to OLE Year 1.

### 3.4. Median group change in BRIEF®2 T-scores from baseline in the core study to OLE Year 1 by MCSF reduction groups

The median change in BRIEF®2 T-scores for the ≥50% MCSF reduction group showed a much larger range of improvements than those in the <50% MCSF reduction group for BRI, ERI, CRI, and GEC; however, this difference was not statistically significant (Table 3).

### 3.5. Proportion of patients who achieved clinically meaningful improvement (RCI values ≥95% certainty) in BRIEF®2 T-scores by MCSF reduction group

A significantly greater proportion of the 45 patients in the ≥50% MCSF reduction group achieved clinically meaningful improvement (RCI values ≥95% certainty) in ERI (n = 10, p = 0.002) and/or in CRI (n = 11, p = 0.001) (Fig. 2) than was noted in the 13 patients in the <50% MCSF group. Only 2 patients showed improvement in both indexes. This suggests that improvement associated with treatment may present differently in different patients. None of the patients in the <50% MCSF group showed clinically meaningful improvement in any of the indexes.

Post-hoc cross-tabulations of the individual scales composing ERI revealed that patients in the ≥50% MCSF reduction group were more likely than those in the <50% MCSF reduction group to show significant, clinically meaningful improvement on the Emotional Control scale (p = 0.02) but not on the Shift scale. Post-hoc cross-tabulations of the individual scales composing CRI revealed that patients in the ≥50% MCSF reduction group were more likely than those in the <50% MCSF reduction group to show significant, clinically meaningful improvement on the Organization of Materials scale (p = 0.01) but not on the Initiate, Working Memory, Plan/Organize, or Task Monitor scale.

Clinical experience indicates that achieving ≥75% MCSF reduction represents a profound clinical effect. Qualitatively, we compared patients who had minimal (<25%) MCSF reduction with those who achieved profound (≥75%) MCSF reduction. Proportionately more patients in the ≥75% MCSF reduction group than in the <25% MCSF reduction group achieved profound improvement (RCI values ≥95% RCI certainty) in ERI, CRI, and GEC (ERI, 31% vs. 0%; CRI, 24% vs. 0%; GEC, 24% vs. 14%; Fig. 3).

### 3.6. Proportion of patients who achieved clinically meaningful worsening (RCI values ≥80% certainty) in BRIEF®2 T-scores by MCSF reduction group

In contrast to clinically meaningful improvement observed in ERI and CRI, there were no significant differences between MCSF...

---

**Table 3**

| BRIEF®2 T-scores by MCSF reduction group | Median T-score at baseline in the core study<sup>a</sup> | Median T-score at OLE Year 1<sup>a</sup> | Median change in T-score from pre-randomization baseline to OLE Year 1<sup>b</sup> |
|----------------------------------------|-----------------|-----------------|----------------------------------|
| Behavior Regulation Index (BRI)        |                 |                 |                                  |
| <50% (n = 13)                          | 72 (61 to 84)   | 71 (50 to 80)   | −2 (−14 to 8)                    |
| ≥50% (n = 45)                          | 64 (37 to 90)   | 66 (37 to 90)   | −4 (−42 to 47)                   |
| Emotion Regulation Index (ERI)         |                 |                 |                                  |
| <50% (n = 13)                          | 63 (45 to 83)   | 66 (44 to 89)   | 2 (−7 to 16)                     |
| ≥50% (n = 45)                          | 61 (39 to 89)   | 61 (39 to 89)   | 0 (−22 to 50)                    |
| Cognitive Regulation Index (CRI)      |                 |                 |                                  |
| <50% (n = 13)                          | 70 (50 to 83)   | 69 (50 to 86)   | −1 (−7 to 14)                    |
| ≥50% (n = 45)                          | 61 (39 to 85)   | 63 (37 to 84)   | −3 (−25 to 45)                   |
| Global Executive Composite (GEC)      |                 |                 |                                  |
| <50% (n = 13)                          | 71 (51 to 84)   | 75 (53 to 85)   | −1 (−11 to 13)                   |
| ≥50% (n = 45)                          | 65 (37 to 90)   | 67 (36 to 88)   | −2 (−31 to 50)                   |

<sup>a</sup>Negative values show improvement. Differences between MCSF reduction groups in BRIEF®2 indexes/composite at, and change from, baseline in the core study and OLE 1 Year were NS (p > 0.05).

<sup>b</sup>BRIEF®2, Behavior Rating Inventory of Executive Function®, Second Edition; MCSF, monthly convulsive seizure frequency; NS, no statistically significant differences among MCSF reduction groups; OLE, open-label extension.
Fig. 1. Overall correlation between percentage change in MCSF and change in BRIEF^2 T-scores from baseline in the core study to OLE Year 1 (N = 58). Scatterplots with a linear fit line of percentage change in seizure frequency by change in BRIEF^2 indexes/composite from baseline in the core study to OLE Year 1. BRI, Behavior Regulation Index; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite; MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

Fig. 2. RCI-defined clinically meaningful changes in BRIEF^2 T-scores from baseline in the core study to OLE Year 1 in children and young adults by MCSF reduction group (<50% vs. ≥50%). Proportion of children and young adults with significant, clinically meaningful improvement in BRIEF^2 indexes/composite at RCI ≥95%. p values are calculated by Somers’ D, <50% and ≥50% MCSF reduction groups. Bold p values show statistical significance. BRI, Behavior Regulation Index; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite; MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

Fig. 3. Subcategorization by MCSF reduction groups by clinical criteria. The proportions of children and young adults achieving clinically meaningful changes in BRIEF^2 indexes/composite from baseline in the core study to OLE Year 1 are shown for profound responders (≥75% MCSF reduction) vs minimal responders (<25% MCSF reduction) at RCI ≥95% certainty. BRI, Behavior Regulation Index; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite; MCSF, monthly convulsive seizure frequency; OLE, open-label extension; RCI, Reliable Change Index.
reduction groups (<50% vs. ≥50%) in the proportion of patients experiencing clinically meaningful worsening (RCI ≥80% certainty) in BRI, ERI, CRI, or GEC.

Additionally, the proportion of patients who showed clinically meaningful worsening (RCI values ≥80% certainty) in BRI, ERI, CRI, and GEC was similar between the ≥75% MCSF reduction group and the <25% MCSF reduction group.

4. Discussion

Poor neurodevelopmental outcomes in people with developmental and epileptic encephalopathies such as DS likely represent an interplay between seizure frequency, age at seizure onset, seizure types, genotype, underlying etiology (i.e., sodium channelopathy), and ASM use [19,21]. A majority of studies have found deficits in intellectual functioning and adaptive behavior in these children [1,14,43,44]. However, measuring intelligence or behavior alone does not fully capture whether a child has the mental skills needed to set goals and accomplish tasks in the real world. Guzetta (2011) [45] noted a need to broaden exploration of the cognitive phenotype in DS beyond intellectual functioning to include EF. EF reflects the self-regulatory abilities that underpin cognitive, behavioral, and emotional functioning. As such, EF may be directly impacted by seizure frequency [46] but may also play a mediating role between treatment with ASMs and cognitive impairment in children with epilepsy [47].

To date, few studies have examined the role of EF in DS. Chieffe et al. (2011) and Acha et al. (2015) [24,48] conducted studies with very small numbers of children and limited assessments. In the only ASM studies that included assessment of EF in children/young adults with DS (Study 1 RCT and Study 1504 RCT), Lagae et al. (2020) and Nabbout et al. (2019) [36,49] found no significant difference between fenfluramine and placebo with regard to worsening of everyday EF after 14 weeks of treatment. On the contrary, one of these studies [36] found significant improvement in fenfluramine-treated groups on some EF indexes after 14 weeks of treatment. The present analysis extended these findings to examine relationships between long-term (≥1 year) reduction in MCSF associated with fenfluramine treatment and improvement in everyday EF as measured by parent/caregiver ratings.

Our study found a positive association between reduced seizure frequency and improved parent/caregiver-rated aspects of everyday EF. Children/young adults with ≥50% MCSF reduction were significantly more likely to show clinically meaningful improvement in ERI and CRI than those who had <50% MCSF reduction (RCI values ≥95% certainty). Substantial and longer-term MCSF reduction was associated with a greater likelihood of clinically meaningful improvement in ERI and CRI. Improvements in ERI reflect more flexible thinking and adapting to new people, things, and situations (Table 1). A child with improvement in ERI scores may have fewer strong emotional outbursts. Improvements in ERI reflect more attentional, less distractibility, and more organization. A child with improvement in CRI scores may remain attentive or may stay focused longer, notice mistakes, or hold information longer in active memory (Table 1). Conversely, BRI reflects impulsive or socially intrusive behavior. Children who score poorly on the BRI have trouble controlling impulses and do not acknowledge how their behavior affects others (Table 1). These findings suggest that substantial reduction in convulsive seizure frequency over extended periods of time may be important for improving everyday EF in children and young adults with DS, particularly emotion regulation and management of cognitive function.

The present findings are consistent with literature showing relationships between reduced seizure frequency and cognitive improvement in people with epilepsy in general. For example, researchers have found that children with drug-sensitive epilepsies performed better on cognitive assessments than children with drug-resistant forms, and these cognitive improvements correlated with seizure control and duration of illness [50]. Additionally, longer seizure duration [51] and higher seizure frequency corresponded to diminished intellectual capacity [52]. More recently, studies have examined EF and have found that it may mediate the relationship between ASM use and cognitive function in children with epilepsy [47]. Studies in children with DS have only begun to explore the potential importance of EF in this multifactorial condition. The only large phase 3 ASM study to date found that treatment with add-on fenfluramine resulted in reduced seizure frequency and improved everyday EF [36]. Our analysis of data from the long-term OLE of this study extends these findings to show a longer term relationship between reduced seizure frequency and improved everyday executive functioning in children and young adults with DS.

To our knowledge, no prospective study in children and young adults with DS or other drug-resistant epilepsy has examined correlations between EF and changes in seizure frequency over time among individual children and young adults. Our study is the first to show a positive association between ASM use and everyday EF in a DS population with inherently high seizure burden at baseline. Although the current analysis focused on changes in seizure frequency and impact on everyday EF, the results cannot rule out the possibility of an additional independent mechanism of action of fenfluramine for everyday EF. It is important to note that the well-known serotonergic effects of fenfluramine—i.e., its effects on the 5HT4 receptor—may also play a role in the positive changes observed in EF and cognition [53–55]. Furthermore, preclinical studies have shown that fenfluramine has positive modulatory activity at sigma-1 receptors, which contributes to both antiseizure activity and positive effects on EF in zebrafish and mouse models [53,55].

Strengths of this study include use of a specific rating scale for assessment of everyday EF that considers behavior regulation, emotion regulation, cognitive regulation, and overall executive functioning. For the most part, assessment of EF in children with DS has relied on performance-based measures in very small samples, preventing thorough statistical analysis and limiting generalizability. In response to the limitations of performance-based measures, rating scales were developed to assess parents'/caregivers' observations of the child's executive functioning in everyday life; BRIEF² as used in this study is one such example [56].

Further, BRIEF² offers RCIs for capturing meaningful change. Utilizing assessments of parent/caregiver perceptions of change in rare disease clinical trials helps to characterize the degree of change that is meaningful to them. The most common metric for determining individual cognitive change has been the unstandardized raw change score (i.e., the difference between a pre-test score and a post-test score) [57,58]. However, this method may reflect practice effects, test-related error, and/or regression to the mean [57], obscuring one's ability to determine when a score change that is statistically significant is also clinically meaningful. RCI evaluates changes in outcome scores following treatment interventions beyond those attributable to test-related error and practice effects. These scores have been widely used to evaluate clinically meaningful change in mental health and behavioral medicine outcomes research and are increasingly becoming an important aspect of defining clinically meaningful cognitive change following treatment interventions in epilepsy populations [59] (NCT01463306).

Limitations of the present study include lack of a matching control group and inclusion of multiple exploratory analyses (increasing the chance of false-positive results or Type 1 errors) [60]. As the study was an open-label add-on of fenfluramine in combination with other ASMs in children and young adults with DS, it was not possible to blind parents/caregivers to the investigational
treatment—a potential source of bias in rating. Further, parent ratings often do not correlate well with performance-based tests of EF in children with epilepsy [61,62], suggesting that the 2 different types of measurement may be tapping different constructs within the EF domain. Numerous covariates may affect the reliability of ratings, including parents’/caregivers’ perceptions, which may be influenced by mood, caregiver burden, or other rater and patient characteristics [41]. As a post-hoc exploratory analysis of data from an RCT, this study was not primarily designed or statistically powered to assess effects of fenfluramine treatment on EF in children and young adults with DS and should be viewed as hypothesis-generating. Additional analyses of data from the remainder of the OLE population are warranted to confirm our findings.

Future directions include adding a matching control group and studying larger populations of fenfluramine-treated children and young adults to permit more finely grained analysis of everyday EF using individual BRIEF2® scales in addition to summary scores. With larger sample sizes, we can evaluate what factors drive changes in EF (i.e., age, concomitant ASM use, seizure type, etc.). Although there is no gold standard battery for assessment of drug effects on EF in children with epilepsy, several performance-based tests are now available to capture specific components of this complex construct [47,63]. Ideally, the parent/caregiver form of BRIEF2® would be combined with performance tests of different aspects of EF to best assess effects of adjunctive fenfluramine on EF in children and young adults with DS. Additionally, examining treatment of children at a younger age may provide a better understanding of the contributions of seizure reduction to early development of EF. The mean age of children and young adults receiving fenfluramine treatment in this subset of patients was 11 years. Study results suggest that earlier initiation of treatment that reduces seizure frequency may better protect development of EFs.

Use of treatments that can reliably provide sustained high levels of seizure frequency reduction along with other interventions for children with DS is likely to result in better longer-term neurodevelopmental outcomes [3]. Based on data from the core study, the number needed to treat (NNT) with fenfluramine to achieve >50% reduction in MCSF was 2 (0.7 mg/kg/day) to 4 (0.2 mg/kg/day) compared to typical NNTs of 8 to 10 reported for other ASMs in refractory epilepsy, meaning fewer patients need to be treated with fenfluramine to identify 1 patient with the level of response associated with improvement in everyday EF in the current analysis [64].

5. Conclusions

In conclusion, our exploratory analysis showed a relationship between seizure frequency reduction and improvement in everyday EF in individuals with DS. Long-term and substantial (>50%) MCSF reduction was associated with a greater likelihood of significant, clinically meaningful levels of improvement in everyday EF, manifested as improvement in emotion regulation and cognitive regulation. Results of our study suggest that long-term treatment with fenfluramine may provide clinically meaningful improvement in everyday EF in this subset of children and young adults with DS (mean age: 11 years; range: 5–18 years). It remains to be seen if earlier adjunctive use of fenfluramine at younger ages, when seizure burden remains high during a critical period of brain development, could result in even more dramatic improvement in EF. Further studies are warranted as larger quantities of patient data at Year 1 and beyond in the OLE become available.

Declaration of Competing Interests

Dr. Bishop is principal consultant for Global Pharma Consultancy, LLC, which has received consultancy fees from Zogenix for research support, and owns shares of Zogenix stock.

Dr. Isquith and Dr. Gioia are associates of Global Pharma Consultancy, LLC, which has received consultancy fees from Zogenix for research support and has received royalties from Psychological Assessment Resources (PAR) for sale of the BRIEF® instruments.

Dr. Gammaitoni, Dr. Galer, and Dr. Farfel are employees of and/or own stock in Zogenix.

Dr. Nabbout received research support from Eisai, GW Pharma, UC-B, and Zogenix; served as a consultant/advisor for Eisai, Biogen, GW Pharma, Novartis, Shire, and Zogenix; and served in a speaker role for Advicencia, Eisai, BioMarin, GW Pharma, Novartis, and Zogenix.

Dr. Wirrell provided contracted research support for Zogenix and GW Pharma; served as a consultant for Biomarin and Encoded Therapeutics; and is an advisor for the Dravet Syndrome Foundation.

Dr. Polster received research support from Zogenix and served as a consultant/speaker for Novartis, Zogenix, Desitin, UCB Pharma, and Shire.

Dr. Sullivan received research grants from Stoke, Marinus, Biopharm, and Zogenix; served as a consultant/advisor for the Dravet Syndrome Foundation, Encoded, Neurocrine, and Epugenix; has stock options in Epugenix; served as a reviewer for the Epilepsy Study Consortium; and received travel support from Zogenix.

Acknowledgments

Zogenix thanks all the children and young adults, their families, and the investigators involved in this study. The authors thank Douglas Haney, PhD, for his role as advisor on statistical methods and for his critical review of text and analysis results. Medical writing and editorial assistance were provided by Danielle Ippolito, PhD, CMP, MWCC, and Dolores Matthews, ELS, of PharmaWrite, LLC (Princeton, NJ, USA), and were funded by Zogenix, Inc.

References

[1] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52(suppl 2):3–8.
[2] Gataullina S, Dulac O. From genotype to phenotype in Dravet disease. Seizure 2017;44:58–64.
[3] Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. Pediatr Neurol 2017;68:18–34.
[4] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde BW, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:1757–62.
[5] Brunklaus A, Zuberi SM. Dravet syndrome—from epileptic encephalopathy to channelopathy. Epilepsia 2014;55:979–84.
[6] Wolff M, Cassé-Perrot C, Dravet C. Severe myoclonic epilepsy of infants (Dravet syndrome): natural history and neuropsychological findings. Epilepsia 2006;47(suppl 2):45–8.
[7] Bayat A, Hjalgrim H, Moller RS. The incidence of SCN1A-related Dravet syndrome in Denmark is 1:22,000: a population-based study from 2004 to 2009. Epilepsia 2015;56:36–9.
[8] Bender AC, Morse RP, Scott RC, Holmes GL, Lenck-Santini PP. SCN1A mutations in Dravet syndrome: impact of interneuron dysfunction on neural networks and cognitive outcome. Epilepsy Behav 2012;23:177–86.
[9] Brunklaus A, Ellis R, Reavey E, Forbes GH, Zuberi SM. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135(pt 8):2329–36.
[10] Clea L, Del-Favero J, Ceulemans B, Lagea L, Van Broeckhoven C, De Jonghe P. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68:1327–32.
[11] Marini C, Scheffer IE, Nabbout R, Saul A, De Jonghe P, Zara F, et al. The genetics of Dravet syndrome. Epilepsia 2011;52(suppl 2):24–9.
[12] Berg AT, Kaisar K, Dixon-Salazar T, Elliot A, McNamara N, Meskis MA, et al. Seizure burden in severe early-life epilepsy: perspectives from parents. Epilepsia Open 2019;4:293–301.
[13] Chieffo D, Battaglia D, Lettori D, Del Re M, Brogna C, Dravet C, et al. Neuropsychological development in children with Dravet syndrome. Epilepsy Res 2011;95:86–93.
[14] Janssen JS, Hallbook T, Reilly C. Intellectual functioning and behavior in Dravet syndrome: a systematic review. Epilepsy Behav 2020;108:107079.
