

RESEARCH ARTICLE

Fenfluramine in the treatment of Dravet syndrome: Results of a third randomized, placebo-controlled clinical trial

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Abstract

Objective: This study was undertaken to assess the safety and efficacy of fenfluramine in the treatment of convulsive seizures in patients with Dravet syndrome.

Methods: This multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 clinical trial enrolled patients with Dravet syndrome, aged 2–18 years with poorly controlled convulsive seizures, provided they were not also receiving stiripentol. Eligible patients who had ≥ 6 convulsive seizures during the 6-week baseline period were randomized to placebo, fenfluramine .2 mg/kg/day, or fenfluramine .7 mg/kg/day (1:1:1 ratio) administered orally (maximum

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dose = 26 mg/day). Doses were titrated over 2 weeks and maintained for an additional 12 weeks. The primary endpoint was a comparison of the monthly convulsive seizure frequency (MCSF) during baseline and during the combined titration–maintenance period in patients given fenfluramine .7 mg/kg/day versus patients given placebo.

Results: A total of 169 patients were screened, and 143 were randomized to treatment. Mean age was 9.3 ± 4.7 years ($\pm$ SD), 51% were male, and median baseline MCSF in the three groups ranged 12.7–18.0 per 28 days. Patients treated with fenfluramine .7 mg/kg/day demonstrated a 64.8% (95% confidence interval = 51.8%–74.2%) greater reduction in MCSF compared with placebo ($p < .0001$). Following fenfluramine .7 mg/kg/day, 72.9% of patients had a $\geq 50\%$ reduction in MCSF compared with 6.3% in the placebo group ($p < .0001$). The median longest seizure-free interval was 30 days in the fenfluramine .7 mg/kg/day group compared with 10 days in the placebo group ($p < .0001$). The most common adverse events ($>15\%$ in any group) were decreased appetite, somnolence, pyrexia, and decreased blood glucose. All occurred in higher frequency in fenfluramine groups than placebo. No evidence of valvular heart disease or pulmonary artery hypertension was detected.

Significance: The results of this third phase 3 clinical trial provide further evidence of the magnitude and durability of the antiseizure response of fenfluramine in children with Dravet syndrome.

KEYWORDS

clinical pharmacology, encephalopathy, epilepsy, seizure

1 | INTRODUCTION

Dravet syndrome (DS) is a rare, severe, treatment-resistant developmental and epileptic encephalopathy.¹ It typically begins at approximately 6 months of age (but its onset has been reported between 12 and 18 months in rare cases)^{2,3} in otherwise normal infants and is characterized by severe seizure burden, including focal and generalized seizures, developmental slowing and regression, cognitive dysfunction, gait abnormalities, and elevated risk of premature mortality, primarily due to status epilepticus and sudden unexpected death in epilepsy (SUDEP).^{1–4} More than 90% of DS patients have a pathogenic loss of function variant in *SCN1A*,^{3,5} the gene that encodes the α -1 subunit of the neuronal voltage-gated sodium channel.^{6,7} Conventional antiseizure medications (ASMs) often provide inadequate seizure control, as illustrated by the observation that 45% of DS patients continue to experience ≥ 4 tonic-clonic seizures each month despite treatment with ≥ 3 ASMs.⁸

Fenfluramine was approved for the treatment of seizures associated with DS in the United States, European Union, and United Kingdom based on the results of two

Key Points

- In patients with Dravet syndrome, fenfluramine treatment resulted in a 65% greater reduction in convulsive seizure frequency than placebo
- Of patients treated with fenfluramine .7 mg/kg/day, 72.9% demonstrated a $\geq 50\%$ reduction in convulsive seizure frequency
- The most common adverse events were consistent with the known safety profile of fenfluramine, including decreased appetite and somnolence
- No incidence of valvular heart disease or pulmonary artery hypertension was observed during the study

previous double-blind, placebo-controlled clinical trials^{6,9} and an open-label extension (OLE) study.^{10,11} In the first study, DS patients not concomitantly treated with stiripentol who were treated with oral fenfluramine

at .7 mg/kg/day (maximum daily dose = 26 mg) experienced a 62.3% greater reduction in monthly convulsive seizure frequency (MCSF) compared with patients treated with placebo ($p < .0001$).⁶ In the second study, all patients received concomitant stiripentol as part of their ASM regimen, and patients who were treated with fenfluramine .4 mg/kg/day (maximum dose = 17 mg/day) demonstrated a 54.0% greater reduction in MCSF compared with placebo-treated patients ($p < .001$).⁹ In both of these double-blind studies, patients demonstrated statistically significant longer seizure-free intervals while treated with fenfluramine than with placebo.^{6,9} These antiseizure responses have been sustained in the OLE study for up to 3 years.^{10,11} In addition to these antiseizure benefits, improvements in everyday executive functions have been reported in both short-term¹² and long-term studies in patients aged 5–18 years.¹³ More recently, significant improvements were also noted in preschool age children (aged <5 years) during the randomized clinical trials.¹⁴ In addition, all-cause mortality and SUDEP incidence in DS patients treated with fenfluramine were substantially lower than literature-reported values.¹⁵

Here, we report the major findings of this third clinical trial of fenfluramine in patients with DS.

2 | MATERIALS AND METHODS

2.1 | Study design

During the fenfluramine development program, two identical phase 3 multinational clinical trials were conducted. Study NCT02682927 enrolled patients in the United States and Canada, and study NCT02826863 enrolled patients in Western Europe and Australia. Because of slow enrollment in both studies, the studies were combined prior to unblinding the results and analysis, and instead split into two separate studies based on dates of enrollment. The initial study included the first 119 patients who entered the studies and were randomized to treatment.⁶ The present study includes the remaining patients (i.e., later dates of enrollment), as well as patients from Japan who enrolled in study NCT02826863 after the two studies were combined. Altogether, approximately 48 sites enrolled patients into the studies. In the present study, the first patient enrolled on February 2, 2017 and the last patient completed the study on July 29, 2020. The study protocols were reviewed and approved by each study site's institutional review board or independent ethics committee prior to study initiation. Before enrolling in the trial, parents or legal guardians provided signed written consent for each patient.

2.2 | Patients

Patients aged 2–18 years with a clinical diagnosis of DS were eligible to enroll in the trial if their seizures were not completely controlled by their current ASM regimen. All patients underwent genetic testing to determine the presence of a likely pathogenic variant of *SCN1A*, but a positive finding was not required for eligibility. The diagnosis of DS for each patient was confirmed by the Epilepsy Study Consortium (<http://epilepsyconsortium.org/>). Patients had to have at least four convulsive seizures per 4-week period during the 12 weeks prior to enrollment, based on medical records or reports of caregivers. In addition, each patient's ASM regimen had to have been stable for at least 4 weeks prior to screening and predicted to remain stable during the trial. Patients receiving stiripentol or any form of cannabidiol, including Epidiolex (which was an investigational drug at the time the present study was initiated), were not eligible for the trial. Other prescreening exclusion criteria included a history of cardiovascular or cerebrovascular disease, aortic or mitral valve regurgitation diagnosed by echocardiography, current treatment with centrally acting anorectic agents or monoamine oxidase inhibitors, or the use of any centrally acting drug with serotonin receptor agonist or antagonist properties. Patients with a positive blood test for cannabidiol or with a positive urine test for tetrahydrocannabinol were excluded from the study.

2.3 | Study procedures

Eligible patients underwent a 6-week baseline period to establish their baseline seizure frequency and eligibility for randomization. During this period, echocardiograms were performed and patients demonstrating any degree of aortic or mitral valve regurgitation, including trace, were excluded from participation in the trial. To qualify for randomization, each patient had to have at least six convulsive seizures during the baseline period, with at least two occurring in the first and last 3 weeks. Seizures were recorded by caregivers with an electronic diary, including date, time of day, seizure type, and duration. Convulsive seizures were defined in this clinical trial as hemiclonic, tonic, clonic, tonic-atonic, generalized tonic-clonic, and focal with clearly observable motor involvement. The incidence of nonconvulsive seizures was also recorded.

At the end of the baseline period, patients meeting the eligibility criteria were randomized to one of three treatments in a 1:1:1 ratio: placebo, fenfluramine .2 mg/kg/day, or fenfluramine .7 mg/kg/day. Treatments were assigned using an interactive web-based response system and added to their baseline standard-of-care regimen. Fenfluramine

dose was limited to a maximum of 26 mg/day. Daily doses were administered orally as two equal doses, one dose in the morning and one dose in the evening, approximately 12 h apart. The randomization schedule was created by an independent statistician and stratified patients by age so that each group had 25% of patients less than 6 years old. The active treatment and placebo were supplied by the sponsor and were of identical appearance and taste. All participants, caregivers, investigators, and study monitors and everyone else involved in the study were blinded to treatment assignment.

Treatment started with a 2-week titration period. Patients in the fenfluramine .7 mg/kg/day group started treatment with a dose of .2 mg/kg/day and were gradually titrated to their assigned dose over 14 days. The other two groups underwent a dummy titration during this period. After completing the titration period, patients remained on their assigned treatment for an additional 12 weeks (maintenance period). Thus, the entire treatment period was 14 weeks (titration + maintenance).

Adverse events were reported from the start of the baseline period through completion of the study, which included a follow-up visit. Clinical laboratory measurements and assessment of vital signs, height, and weight were done at each in-clinic study visit. An evaluation of cognitive function at baseline and during treatment was performed using the Behavior Rating Inventory of Executive Function (BRIEF) or BRIEF-P for patients under 6 years old.¹⁶ This assessment was included as a safety endpoint due to the association of some ASMs with adverse effects on cognition. The BRIEF instrument was administered during the baseline period and after 7 and 14 weeks of treatment.

Because of the reported incidence of valvular heart disease (VHD) in obese adults who were treated with fenfluramine as a weight-loss drug (for review, see Schoonjans et al.¹⁷), all patients underwent serial echocardiographic examinations during the study. These examinations were done during the baseline period and after 6 and 14 weeks of treatment. The echocardiograms were evaluated by two cardiologists who were aware that fenfluramine was being tested, but were blinded to treatment assignment of individual patients. A third blinded cardiologist served as an arbiter in the event of disagreement between the two primary evaluators. Cardiac valve regurgitation was graded as absent, trace, mild, moderate, or severe based on accepted guidelines.¹⁸ Mitral valve regurgitation of moderate or greater severity and/or aortic valve regurgitation of mild or greater severity was considered evidence of VHD, provided one or more of the following was also observed on echocardiography: structural lesion or restriction of valve movement of the aortic or mitral valve, abnormal left ventricular function with low left ventricular ejection

fraction, and/or left ventricular dilation or left atrial enlargement. Pulmonary artery systolic pressure (PASP) was estimated from the peak systolic Doppler-determined tricuspid regurgitation jet velocity, and pulmonary artery hypertension (PAH) was defined as PASP > 35 mmHg.

2.4 | Outcomes

MCSF was expressed as seizures per 28 days, and the primary endpoint was a comparison of the change in mean MCSF from baseline and the titration–maintenance period in patients treated with fenfluramine .7 mg/kg/day compared with patients treated with placebo. Key secondary outcomes included a similar comparison for patients treated with fenfluramine .2 mg/kg/day, comparison of both fenfluramine groups with placebo for the percentage of patients achieving $\geq 50\%$ reduction in mean MCSF, and comparison of the longest seizure-free intervals seen in each group. Other secondary outcomes included a responder analysis of patients in each group who achieved $\geq 25\%$, $\geq 75\%$, or 100% reduction in mean MCSF and the Clinical Global Impression of Improvement (CGII). The CGII solicited a response from the investigator and the caregivers on a 7-point Likert-like scale ranging from “very much improved” to “very much worse.”

Change in quality of life (QOL) was assessed with two instruments: the Quality of Life in Childhood Epilepsy Scale¹⁹ and Pediatric Quality of Life Inventory.²⁰ The Quality of Life in Childhood Epilepsy Scale interrogates how epilepsy affects activities of daily life, and the Pediatric Quality of Life Inventory assesses physical, emotional, social, and school functioning. Both instruments report scores on a scale of 0–100, with higher scores representing better QOL.

2.5 | Statistical analysis

The statistical analysis plan was written specifically for the merged clinical trial before completion of treatment and unblinding. The power analysis assumed that the percentage change in MCSF would have an SD of 55%, which was based on results of previous studies of stiripentol^{21,22} and cannabidiol²³ in the treatment of DS. This assumption led to a sample size per treatment arm of 40 patients, resulting in 90% power to detect a 40% difference between treatment groups in mean change in MCSF from baseline at the .05 level.

An analysis of covariance (ANCOVA) model was used to analyze the primary endpoint. Treatment (three levels) and age group (<6 years and ≥ 6 years) were factors, log baseline MCSF was a covariate, and log MCSF during the

combined titration and maintenance periods was the response. The same analysis was used for the first key secondary endpoint, a comparison of the .2 mg/kg/day group with placebo for change from baseline in MCSF. The proportion of patients in each treatment arm who achieved a $\geq 50\%$ reduction in MCSF (key secondary endpoints) was analyzed with a logistic regression model using the same factors used in the primary analysis. The longest seizure-free intervals during treatment compared to placebo (key secondary endpoints) were assessed with a Wilcoxon rank sum test. The median difference between groups and 95% confidence intervals (CIs) were estimated with the Hodges–Lehman method. A serial gatekeeping strategy²⁴ was employed to maintain the type 1 error rate of .05 for pairwise comparison of the primary and key secondary endpoints. No imputation was done for missing data.

The modified intent-to-treat population comprised all patients who received at least one dose of study medication and completed at least 1 week of seizure diary records after starting treatment, and it served as the analysis population for all primary and key secondary endpoints. The safety population included all patients who received at least one dose of study medication.

3 | RESULTS

Patient disposition is shown in Figure 1. From February 2, 2017 to July 29, 2020, a total of 169 patients were screened for eligibility, and 143 were randomized to treatment. The primary reasons for screen failure were <6 convulsive seizures during the baseline period ($n=8$), cardiovascular or cardiopulmonary abnormalities ($n=5$), or failure to meet randomization criteria during the baseline period ($n=13$). One hundred forty-three patients were randomized to treatment: placebo ($n=48$), fenfluramine .2 mg/kg/day

($n=46$), and fenfluramine .7 mg/kg/day ($n=49$). Nine patients withdrew prior to completing the study: five in the placebo group, one in the fenfluramine .2 mg/kg/day group, and three in the fenfluramine .7 mg/kg/day group (Figure 1). The primary reasons cited for withdrawal are shown in Figure 1. Median treatment compliance during the trial, as measured by residual volume of study drug solution in returned bottles at each study visit, was 99.5% in each treatment group.

Patient demographics are shown in Table 1. No clinically important differences in baseline characteristics were observed between the three treatment groups. The mean age of randomized patients in the trial was 9.3 ± 4.7 years. All patients were receiving one or more ASMs, with clobazam and valproate (any form) most commonly used. No patients were treated with vagal nerve stimulation or a ketogenic diet during the study. The median MCSF ranged from 12.7 to 18.0 per month.

Efficacy endpoints are presented in Table 2. The study met its primary efficacy endpoint; patients in the fenfluramine .7 mg/kg/day group demonstrated a 64.8% greater reduction (95% CI = 51.8%–74.2%) in mean MCSF compared with placebo ($p < .0001$). Similarly, the fenfluramine .2 mg/kg/day group had a 49.9% greater decrease in mean MCSF compared with placebo (95% CI = 31.3%–63.4%, $p < .0001$). These beneficial results are also illustrated by the median percent changes in MCSF from baseline to the 14-week titration and maintenance treatment period of -73.7% , -47.0% , and -7.6% in the fenfluramine .7 mg/kg/day, fenfluramine .2 mg/kg/day, and placebo groups, respectively ($p < .0001$ for comparison of each fenfluramine dose with placebo). Significantly more patients treated with either dose of fenfluramine demonstrated $\geq 25\%$, $\geq 50\%$, and $\geq 75\%$ reductions in MCSF compared with placebo (Table 2, Figure 2). For example, 35 patients (73%) treated with fenfluramine .7 mg/kg/day

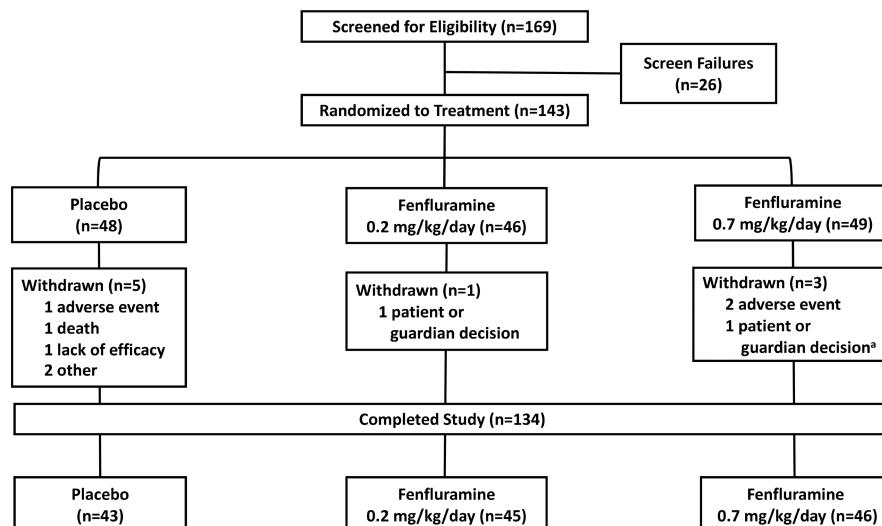


FIGURE 1 Patient disposition.

*This patient was randomized but not treated.

TABLE 1 Patient demographics and other baseline characteristics.

Characteristic	Fenfluramine .7 mg/kg/day, <i>n</i> = 48	Fenfluramine .2 mg/kg/day, <i>n</i> = 46	Placebo, <i>n</i> = 48	Total, <i>n</i> = 142
Age, years				
Mean ± SD	9.4 ± 5.3	9.6 ± 4.4	9.0 ± 4.3	9.3 ± 4.7
Median	9.0	10.0	8.0	9.0
Age group, <i>n</i> (%)				
<6 years	13 (27%)	12 (26%)	11 (23%)	36 (25%)
≥6 years	35 (73%)	34 (74%)	37 (77%)	106 (75%)
Sex, <i>n</i> (%)				
Female	26 (54%)	22 (48%)	21 (44%)	69 (49%)
Male	22 (46%)	24 (52%)	27 (56%)	73 (51%)
Body weight, kg				
Mean ± SD	31.8 ± 16.2	34.4 ± 18.7	33.9 ± 15.3	33.4 ± 16.7
BMI, kg/m ²				
Mean ± SD	17.7 ± 3.6	18.3 ± 4.5	19.5 ± 4.3	18.5 ± 4.2
Region, <i>n</i> (%)				
USA and Canada	19 (40%)	18 (39%)	18 (38%)	55 (39%)
Europe and Australia	23 (48%)	26 (57%)	25 (52%)	74 (52%)
Japan	6 (12%)	2 (4%)	5 (10%)	13 (9%)
Race, <i>n</i> (%)				
White	33 (69%)	37 (80%)	36 (75%)	106 (75%)
Black or African American	1 (2%)	1 (2%)	0	2 (1%)
Asian	8 (17%)	5 (11%)	7 (15%)	20 (14%)
Other, not reported, or unknown ^a	6 (13%)	3 (7%)	5 (10%)	14 (10%)
SCN1A mutation, <i>n</i> (%)	43 (90%)	41 (89%)	44 (92%)	128 (90%)
Concomitant antiseizure medications, <i>n</i> (%)				
Clobazam	29 (60%)	19 (41%)	32 (67%)	80 (56%)
Levetiracetam	13 (27%)	14 (30%)	13 (27%)	40 (28%)
Topiramate	15 (31%)	10 (22%)	13 (27%)	38 (27%)
Valproate [all forms]	26 (54%)	28 (61%)	28 (58%)	82 (58%)
Baseline MCSF				
Mean ± SD	96.4 ± 388.6	67.7 ± 221.2	24.5 ± 35.6	
Median	13.0	18.0	12.7	
Minimum, maximum	2.7, 2701	4.0, 1464	4.0, 229	

Abbreviations: BMI, body mass index; MCSF, monthly convulsive seizure frequency.

^aNot reported or missing; privacy laws in some regions preclude disclosure of certain personal information.

($p < .0001$ compared with placebo) and 21 patients (46%) treated with .2 mg/kg/day ($p = .0001$) had at least a 50% reduction in MCSF, compared with only three patients (6%) treated with placebo. Patients treated with either fenfluramine dose also experienced significantly longer seizure-free intervals compared with patients treated with placebo (Table 2). A total of six patients in the fenfluramine .7 mg/kg/day group were seizure-free for the entire titration and maintenance periods, whereas no patients in the placebo or .2 mg/kg/day groups experienced

seizure freedom (Table 2). In addition, eight patients in the fenfluramine .7 mg/kg/day group experienced a single convulsive seizure during the titration and maintenance periods. No patients in the fenfluramine .2 mg/kg/day or placebo groups experienced near seizure freedom during treatment. Thus, 29% of patients treated with .7 mg/kg/day fenfluramine achieved a state of “near seizure freedom” during treatment (defined as experiencing zero or one convulsive seizure during the titration and maintenance periods⁶).

TABLE 2 Efficacy outcomes.

Outcome	Fenfluramine .7 mg/kg/day, <i>n</i> = 48	Fenfluramine .2 mg/kg/day, <i>n</i> = 46	Placebo, <i>n</i> = 48
Primary and key secondary endpoints ^a			
Change in convulsive seizure frequency per 28 days			
Estimate of % difference from placebo (95% CI) ^b	−64.8 (−51.8 to −74.2)	−49.9 (−31.3 to −63.4)	
<i>p</i>	<.0001	<.0001	
Responder analysis: ≥50% reduction in MCSF			
<i>n</i> (%)	35 (72.9%)	21 (45.7%)	3 (6.3%)
<i>p</i>	<.0001	.0001	
Longest seizure-free interval, days			
Mean ± SD	43.0 ± 33.6	24.0 ± 19.9	13.3 ± 10.9
Median (range)	30 (2–104)	18.5 (2–100)	10 (2–65)
Estimate of median treatment difference (95% CI)	23.5 (9 to 38)	7.5 (4 to 11)	
<i>p</i>	<.0001	.0002	
Other secondary endpoints			
≥25% reduction in convulsive seizure frequency, <i>n</i> (%)	40 (83.3%)	33 (71.7%)	13 (27.1%)
<i>p</i>	<.0001	<.0001	
≥75% reduction in convulsive seizure frequency, <i>n</i> (%)	23 (47.9%)	13 (28.3%)	2 (4.2%)
<i>p</i>	<.0001	.0047	
100% reduction in convulsive seizure frequency, <i>n</i> (%) ^c	6 (12.5%)	0	0
Days of rescue medication use per 28 days during treatment, median (range)			
Baseline	1.33 (0 to 20)	2.0 (0 to 19.3)	.67 (0 to 22.7)
Titration + maintenance periods	0 (0 to 18.2)	.57 (0 to 24.9)	.71 (0 to 19.9)
<i>p</i> ^d	.0001	.0778	
Convulsive seizure frequency per 28 days			
Percent change from baseline, median (range)	−73.7% (−100 to +795)	−47.0% (−97 to +57)	−7.6% (−83 to +143)
<i>p</i> ^e	<.0001	<.0001	
Total seizure frequency per 28 days at baseline			
Median	31.7	25.0	24.7
Percent change from baseline, median	−65.9%	−40.9%	−8.6%
<i>p</i> ^e	<.0001	.0004	
Other seizure frequency per 28 days			
Patients experiencing other seizure types, <i>n</i> (%) ^f	30 (62%)	25 (54%)	26 (54%)
Median	10.7	4.0	15.2
Percent change from baseline, median	−76.8%	−46.2%	−21.0%
<i>p</i> ^e	.0386	.3008	
Change in body weight, kg, median (range, <i>n</i>)			
Age group			
<6 years	−.14 (−1.30 to .77, <i>n</i> = 13)	−.20 (−2.8 to 1.5, <i>n</i> = 12)	.68 (−1.6 to 2.0, <i>n</i> = 11)
≥6 years	−.99 (−9.8 to 3.2, <i>n</i> = 34)	.00 (−7.2 to 3.7, <i>n</i> = 34)	.90 (−1.9 to 6.0, <i>n</i> = 35)

(Continues)

TABLE 2 (Continued)

Outcome	Fenfluramine .7 mg/kg/day, <i>n</i> = 48	Fenfluramine .2 mg/kg/day, <i>n</i> = 46	Placebo, <i>n</i> = 48
Clinical Global Impression of Improvement, <i>n</i> (%) ^g			
Parent/caregiver rating			
“Very much improved” or “much improved”	30 (62%)	16 (35%)	4 (8%)
<i>p</i>	<.0001	.0018	
Investigator rating			
“Very much improved” or “much improved”	31 (65%)	17 (37%)	4 (8%)
<i>p</i>	<.0001	.0019	
Quality of Life in Childhood Epilepsy—Overall Quality of Life ^h			
Baseline, mean ± SD	41.4 ± 9.9	38.7 ± 10.6	39.2 ± 13.7
Change from baseline, mean ± SD	5.5 ± 13.2	6.1 ± 12.5	1.2 ± 9.0
<i>p</i>	.0445	.0790	
Quality of Life, Pediatric Quality of Life Inventory Total Score ^h			
Baseline, mean ± SD	50.8 ± 15.8	47.4 ± 14.0	48.8 ± 16.9
Change from baseline, mean ± SD	2.1 ± 14.7	4.2 ± 17.6	1.9 ± 13.3
<i>p</i>	.9081	.7443	
Executive Function, BRIEF ^{i,j}			
Behavioral regulation index			
Baseline, mean ± SE	73.6 ± 2.5	72.7 ± 2.9	73.3 ± 2.7
Change from baseline, mean ± SE (90% CI)	1.5 ± 2.8 (−2.1 to 5.1)	−3.9 ± 1.7 (−6.1 to −1.7)	−.6 ± 1.4 (−2.4 to 1.2)
<i>p</i>	.595	.215	
Metacognition index			
Baseline, mean ± SE	114.3 ± 3.9	108.7 ± 4.7	106.1 ± 3.8
Change from baseline, mean ± SE (90% CI)	−5.9 ± 4.4 (−11.8 to −.1)	−5.1 ± 2.7 (−8.7 to −1.5)	.0 ± 2.2 (−2.8 to 2.8)
<i>p</i>	.553	.047	
Global executive composite			
Baseline, mean ± SE	187.8 ± 5.9	181.4 ± 7.4	179.5 ± 6.1
Change from baseline, mean ± SE (90% CI)	−4.4 ± 6.7 (−13.2 to 4.3)	−9.0 ± 3.8 (−13.9 to −4.1)	−.6 ± 2.9 (−4.3 to 3.2)
<i>p</i>	1.000	.049	

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; CI, confidence interval; MCSF, monthly convulsive seizure frequency.

^aA hierarchal gatekeeping procedure was used to maintain the simultaneous type 1 error rate at $\alpha = .05$ across the analyses of the primary and five key secondary endpoints.

^bResults are based on an analysis of covariance model with treatment group (three levels) and age group (<6 years, ≥6 years) as factors, log baseline seizure frequency as a covariate, and log seizure frequency during the treatment period (titration + maintenance) as response. The *p*-values were obtained from this model.

^cBecause of the small number of patients demonstrating 100% reduction in seizure frequency, model statistics are not reported.

^dThe change in number of days of rescue medication use between baseline and titration + maintenance periods was assessed for the difference between fenfluramine groups and placebo by a nonparametric analysis of the ranked changes from baseline.

^eProbability value estimated by nonparametric analysis of covariance with treatment group (three levels) and age group (<6 years, ≥6 years) as factors, rank of baseline convulsive seizure frequency as a covariate, and rank of percentage change from baseline of convulsive seizure frequency during titration + maintenance as a response.

^fOther seizure types included focal seizures without clearly observable motor signs, absence or atypical absence, myoclonic, atonic, and other or unclassifiable.

^gProbability value estimated by the Cochran–Mantel–Haenszel test with age group as a stratification factor.

^hIncreases in total score indicate improvement.

ⁱBecause some countries do not have normative populations for BRIEF, only raw scores are presented here.

^jNegative scores indicate an improvement.

FIGURE 2 Cumulative response curves for percent reduction in convulsive seizure frequency during the combined titration and maintenance treatment periods. The vertical dashed lines represent 25%, 50%, and 75% seizure reduction thresholds. The percentage of patients meeting or exceeding these thresholds, along with the odds ratio (OR) and *p*-values compared to placebo, are shown in this figure. FFA, fenfluramine.

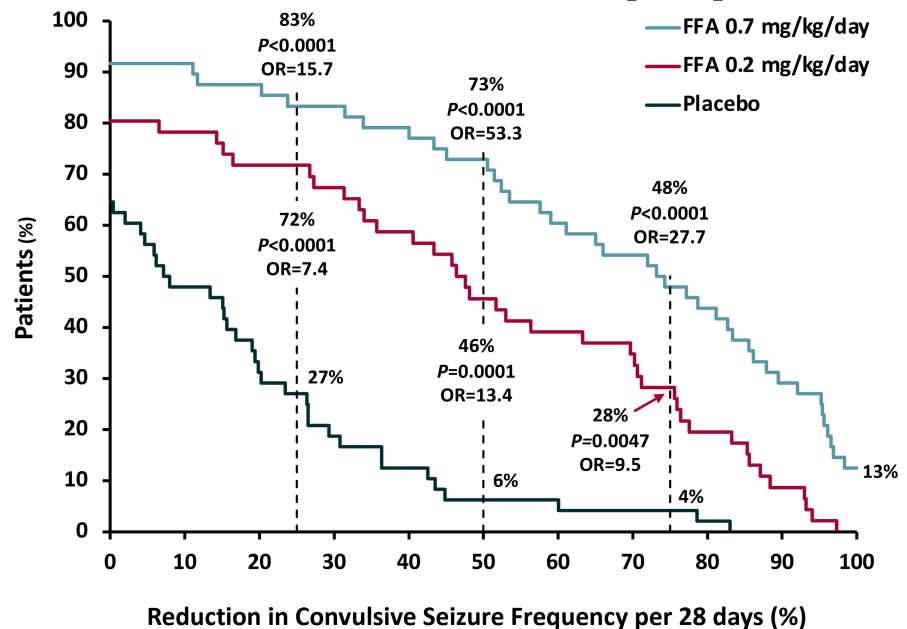


TABLE 3 Noncardiovascular adverse events occurring in $\geq 10\%$ of patients in any treatment group.

Adverse event	Fenfluramine .7 mg/kg/day	Fenfluramine .2 mg/kg/day	Placebo
≥ 1 adverse event	44 (92%)	42 (91%)	40 (83%)
Diarrhea	7 (15%)	7 (15%)	4 (8%)
Fatigue	5 (10%)	3 (6%)	1 (2%)
Pyrexia	9 (19%)	5 (11%)	4 (8%)
Nasopharyngitis	1 (2%)	4 (9%)	5 (10%)
Blood glucose decreased	8 (17%)	11 (24%)	6 (12%)
Decreased appetite	18 (38%)	12 (26%)	3 (6%)
Somnolence	10 (21%)	5 (11%)	5 (10%)
Tremor	6 (12%)	1 (2%)	1 (2%)

Note: Data are presented as *n* (%).

A total of 57% of patients in the trial also experienced other nonconvulsive seizure types, including myoclonic, absence or atypical absence, focal without clear observable motor signs, atonic, or other. During fenfluramine treatment, patients in the .7 mg/kg/day group demonstrated a median 77% decrease in the monthly frequency of nonconvulsive seizures compared to a decrease of 21% in the placebo group ($p=.0386$; Table 2). Patients treated with fenfluramine .2 mg/kg/day experienced a median 46% decrease in the monthly frequency of nonconvulsive seizures, which was not significantly different from that observed in the placebo group (Table 2).

At the end of the treatment period, caregivers rated 62% ($p<.0001$), 35% ($p=.0018$), and 8% of patients in the fenfluramine .7 mg/kg/day, fenfluramine .2 mg/kg/day, and placebo groups, respectively, as “much improved” or “very much improved” (Table 2). The ratings provided by the investigators were virtually identical (Table 2). Change

from baseline in the overall score on the Quality of Life in Childhood Epilepsy Scale was statistically significantly greater than placebo for the fenfluramine .7 mg/kg/day group ($p=.0445$; Table 2) and numerically greater but not statistically significantly different ($p=.0790$) from placebo for the fenfluramine .2 mg/kg/day group. However, on Pediatric Quality of Life Inventory total score, no significant changes were observed in patients treated with either fenfluramine dose compared with placebo.

A summary of treatment-emergent adverse events (TEAEs) occurring in $\geq 10\%$ of patients in any treatment group is presented in Table 3; the most common ($\geq 10\%$) TEAEs reported in fenfluramine-treated patients were diarrhea, fatigue, pyrexia, decreased blood glucose, decreased appetite, somnolence, and tremor. In general, these TEAEs had a higher incidence in the fenfluramine groups than in the placebo group. One death, deemed to be probable SUDEP, occurred in a placebo-treated patient

(a description of this case is reported in the supplemental materials of Cross et al.¹⁵). The majority of TEAEs were of mild or moderate severity for all three treatment groups, including decreased blood glucose, which was assessed as mild in severity and deemed not related to study treatment in all cases. Overall, severe TEAEs were reported for one (2.1%) subject in the placebo group, four (8.7%) subjects in the fenfluramine .2 mg/kg/day group, and three (6.3%) subjects in the fenfluramine .7 mg/kg/day group. Eight patients experienced ≥ 1 serious adverse event (SAE), including two patients in the placebo group, three patients in the fenfluramine .2 mg/kg/day group, and three patients in the fenfluramine .7 mg/kg/day group. The SAEs included infections ($n=1$ in each treatment group), injuries ($n=1$ in each fenfluramine group), status epilepticus ($n=1$ in the fenfluramine .2 mg/kg/day group), and elevated hepatic enzymes ($n=1$ in the fenfluramine .7 mg/kg/day group). Based on the BRIEF results, no worsening of executive function in patients treated with fenfluramine compared with placebo was observed (Table 2).

Because of the history of fenfluramine's use at higher doses as a weight-loss drug, body weight was carefully monitored during the trial. Median body-weight changes are shown in Table 2. Decreased body weight was infrequently reported as a TEAE (0 [0%], one [2.2%], and four [8.3%] patients in the placebo, fenfluramine .2 mg/kg/day, and .7 mg/kg/day groups, respectively). Body-weight losses of $\geq 7\%$ from baseline (a threshold chosen to identify meaningful changes in body weight) were observed for one patient (2%) in the placebo group, four patients (9%) treated with fenfluramine .2 mg/kg/day, and 14 patients (29%) treated with fenfluramine .7 mg/kg/day. No incidence of VHD or PAH was observed during serial Doppler echocardiograms performed during the study.

4 | DISCUSSION

In this third randomized, placebo-controlled clinical trial of add-on fenfluramine for the treatment of seizures associated with DS, patients treated with fenfluramine demonstrated significant reductions in MCSF compared with placebo-treated patients, with the antiseizure responses showing an apparent dose-response relationship. In patients treated with fenfluramine .7 mg/kg/day, 73% experienced a clinically meaningful reduction ($\geq 50\%$) in MCSF and 48% had a profound ($\geq 75\%$) decrease in MCSF. Patients treated with fenfluramine also experienced significantly longer seizure-free intervals than patients in the placebo group. Importantly, at the end of the study, both caregivers and investigators rated a greater proportion of patients treated with fenfluramine than with placebo as "much" or "very much" improved compared to the baseline period.

Selected improvements in QOL measures were also observed in fenfluramine-treated subjects. Fenfluramine was generally well tolerated, as evidenced by the low dropout rate and the spectrum of TEAEs reported during the trial.

The results of the present study confirm and extend prior experience with the use of fenfluramine for the treatment of DS. In the present study and each of the other two phase 3, double-blind clinical trials of fenfluramine in the treatment of DS, large and highly statistically significant reductions in MCSF were observed in patients treated with fenfluramine.^{6,9} Importantly, the antiseizure response to fenfluramine was durable and sustained, not only to the end of the double-blind studies, but also throughout patient participation in the OLE study, a period of up to 3 years (median = 2 years).^{10,11} Additional confirmation of the profound antiseizure response to fenfluramine is provided by two cohorts of DS patients treated with open-label fenfluramine for up to 30 years,²⁵⁻²⁸ as well as the positive results of patients treated in the European Early Access Program.²⁹

The statistically significant improvements in everyday executive function noted in patients treated with .7 mg/kg/day fenfluramine in the initial clinical trial of fenfluramine in DS⁶ were not observed in the present study. It is important to note that the BRIEF instrument was included in these studies as a safety endpoint to detect possible worsening of cognitive function as has been observed with other ASMs. No worsening of everyday executive function based on the BRIEF raw scores has been seen in patients treated with fenfluramine in any of the phase 3 clinical trials of fenfluramine.^{6,9}

Fenfluramine had previously been marketed globally as an anorectic agent to aid in weight loss in obese adults. The drug was used at doses of 60–120 mg/day and was often combined with phentermine. In 1997, following publication of reports of valvular dysfunction in patients who had received fenfluramine,³⁰ the drug was withdrawn from global markets. Subsequent controlled and uncontrolled, mostly retrospective, studies reported a wide range of incidence of VHD in obese adult patients who had been treated with fenfluramine (for review, see Schoonjans et al.¹⁷ and Agarwal et al.³¹). Because of these reports of an association between fenfluramine and VHD, all patients in this and other clinical trials in the clinical development program of fenfluramine in DS were carefully monitored with serial color Doppler echocardiography. No incidence of VHD has been observed in any of the three double-blind clinical trials,^{6,9} nor during up to 3 years of treatment in the OLE study.³¹ In addition, no PAH has been observed in any patients in the phase 3 development program.^{6,9,10}

Adverse events or outcomes associated with fenfluramine (e.g., appetite suppression) could theoretically unblind the study for some patients. The study was too short

to yield information about long-term efficacy and tolerability of fenfluramine for the treatment of DS. However, most patients with DS who completed this or other double-blind studies of fenfluramine have enrolled in an OLE study, during which it was demonstrated that the benefits of fenfluramine have been sustained for a median of 631 days.¹¹

This randomized, placebo-controlled clinical trial showed that fenfluramine added to existing ASMs in children and adolescents with DS resulted in statistically significant and clinically meaningful reductions in MCSF. The most common adverse events were consistent with known effects of fenfluramine, including decreased appetite and somnolence. No incidence of VHD or PAH was observed during the study. The results of this third clinical trial further confirm the robust antiseizure response of fenfluramine in the treatment of DS.

AUTHOR CONTRIBUTIONS

Joseph Sullivan and Lieven Lagae had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Joseph Sullivan, Lieven Lagae, Berten Ceulemans, Michael Lock, Gail M. Farfel, Bradley S. Galer, Arnold R. Gammaioni. Collection, management, analysis, and interpretation of the data: all authors. Drafting of the manuscript: Joseph Sullivan, Lieven Lagae, Berten Ceulemans, Ingrid E. Scheffer, Bradley S. Galer, Arnold R. Gammaioni. Critical review of the manuscript for important intellectual content: all authors. Statistical analysis: Michael Lock, Gail M. Farfel, Bradley S. Galer. Obtained funding: Gail M. Farfel.

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CONFLICT OF INTEREST STATEMENT

J.S. is an advisor and has received research grants from Zogenix (with travel support), Stoke Therapeutics,

Marinus, and Biopharm; is a member of the Dravet Syndrome Foundation Board of Directors; has equity interest in Epygenix Therapeutics; and has served as a consultant/advisor for Epygenix, Encoded, GW Pharma, Asceneuron, Longboard Pharmaceuticals, Knopp Biosciences, and Neurocrine, and as a reviewer for the Epilepsy Study Consortium. L.Lag. and B.C. were advisors to and received grants and fees from Zogenix; they have held the patent for use of fenfluramine to treat Dravet syndrome, which was transferred to their institution and licensed to Zogenix. They and KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by KU Leuven University/Antwerp University Hospital. In addition, B.C. has received research funding from and has been a consultant for Brabant and Zogenix. J.H.C. has acted as an investigator for studies with GW Pharma, Ovid Therapeutics, Zogenix, Vitaflor, Marinus, and Stoke Therapeutics. She has been a speaker and on advisory boards for GW Pharma, Zogenix, Biocodex, Takeda, UCB, and Nutricia; all remuneration has been paid to her department. She holds an endowed chair at UCL Great Ormond Street Institute of Child Health; she holds grants from the National Institute of Health Research (NIHR), EPSRC, GOSH Charity, ERUK, Waterloo Foundation, NIHR Biomedical Research Centre at Great Ormond Street Hospital, Zogenix, Marinus, GW Pharma, and Vitaflor; she is chair of the medical board for DravetUK, Hope for Hypothalamic Hamartoma, and Matthew's Friends. O.D. has received research funding from Novartis, PTC Therapeutics, Zogenix, and Greenwich Pharmaceuticals; and has equity interest at Rettco, Pairnomix, Tilray, Papa & Barkley, California Cannabis Enterprises, Tevard Biosciences, Regal Biosciences, Script Biosciences, Silver Spike Capital, and Silver Spike SPAC. R.G. has received research grants from Zogenix and has served as a speaker/consultant for Zogenix, Biocodex, Novartis, BioMarin, and GW Pharma, and as an investigator for Biocodex, UCB, Angelini, and Eisai. K.G.K. has received research grants from Zogenix, the Pediatric Epilepsy Research Foundation, the Colorado Department of Public Health, and West Therapeutics, and has been a data and safety monitoring board member for Greenwich Pharmaceuticals. L.Lau. has received research grants from Zogenix and GW Pharma. M.N. has received funding from Zogenix. T.P. has received research funding from Zogenix and has been a consultant and speaker for Desitin, Takeda, UCB, and Zogenix. D.T. has received research funding from Zogenix, grants from Zogenix, and personal fees from Eisai and Sunovion. R.N. has received research support from Zogenix, GW Pharma, Eisai, and

UCB; 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. G.M.F., B.S.G., A.R.G., and A.A. were employees of Zogenix at the time of conduct of the present clinical study, but have no current relationships with UCB, the current owner of Fintepla. M.L. reports receiving personal fees from, owning stock in, and being an employee of Zogenix, with patents pending, as well as being an independent consultant for Zogenix. I.E.S. has served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, RogCon, Takeda Pharmaceuticals, UCB, and Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, LivaNova, and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, BioMarin, and Eisai; has served as an investigator for Anavex Life Sciences, Cerecin, Cerevel Therapeutics, Eisai, Encoded Therapeutics, Epiminder, Epygenix, ES Therapeutics, GW Pharma, Marinus, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix, and Zynerba; has consulted for Atheneum Partners, Care Beyond Diagnosis, Epilepsy Consortium, Ovid Therapeutics, UCB, and Zynerba Pharmaceuticals; and is a nonexecutive director of Bellberry and a director of the Australian Academy of Health and Medical Sciences and the Australian Council of Learned Academies. She may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics and licensed to various diagnostic companies; and has a patent for a molecular diagnostic/theranostic target for benign familial infantile epilepsy: [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012-009).

TRIAL REGISTRATION

[ClinicalTrials.gov](https://clinicaltrials.gov): NCT02682927, NCT02826863.

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MEETING PRESENTATIONS

Sullivan J, Lagae L, Cross JH, et al. Fenfluramine (FINTEPLA) in Dravet syndrome: results of a third randomized, placebo-controlled clinical trial (study 3). Presented at: American Epilepsy Society Annual Meeting; December 4–8, 2020; virtual.

Sullivan J, Lagae L, Cross JH, et al. Fenfluramine (FINTEPLA) in Dravet syndrome: results of a third randomized, placebo-controlled clinical trial (study 3). Presented at: Connections: Association of British Neurologists Meeting; April 29–May 21, 2021; virtual.

Sullivan J, Lagae L, Cross JH, et al. Fenfluramine (FINTEPLA) in Dravet syndrome: results of a third randomized, placebo-controlled clinical trial (study 3). Presented at: 13th International Epilepsy Colloquium; May 20–22, 2021; virtual.

Sullivan J, Lagae L, Cross JH, et al. Fenfluramine (FINTEPLA) in Dravet syndrome: results of a third randomized, placebo-controlled clinical trial (study 3). Presented at: Academy of Managed Care Pharmacy Nexus; October 18–21, 2021; Denver, CO.

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REFERENCES

1. Dravet C. The core Dravet syndrome phenotype. *Epilepsia*. 2011;52(suppl 2):3–9.
2. Cetica V, Chiari S, Mei D, Parrini E, Grisotto L, Marini C, et al. Clinical and genetic factors predicting Dravet syndrome in infants with *SCN1A* mutations. *Neurology*. 2017;88(11):1037–44.
3. Li W, Schneider AL, Scheffer IE. Defining Dravet syndrome: an essential pre-requisite for precision medicine trials. *Epilepsia*. 2021;62(9):2205–17.
4. Cooper MS, McIntosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, et al. Mortality in Dravet syndrome. *Epilepsy Res*. 2016;128:43–7.
5. Claes L, Del-Favero J, Ceulemans B, Lagae 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(6):1327–32.
6. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2019;394(10216):2243–54.
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(4):e36–9.

8. Aras LM, Isla J, Mingorance-Le MA. The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome. *Epilepsy Behav.* 2015;44:104–9.
9. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, et al. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. *JAMA Neurol.* 2020;77(3):300–8.
10. Sullivan J, Scheffer IE, Lagae L, Nabbout R, Pringsheim M, Talwar D, et al. Fenfluramine HCl (Fintepla®) provides long-term clinically meaningful reduction in seizure frequency: analysis of an ongoing open-label extension study. *Epilepsia.* 2020;61(11):2396–404.
11. Scheffer IE, Devinsky O, Perry MS, Wheless J, Thiele EA, Wirrell E, et al. Efficacy and tolerability of adjunctive FINTEPLA (fenfluramine HCl) in an open-label extension study of Dravet syndrome patients treated for up to 3 years [poster]. Presented at American Epilepsy Society annual meeting, December 4–8, 2020. Virtual Meeting.
12. Bishop KI, Gioia GA, Isquith PK, Gammaitoni AR, Farfel G, Galer BS, et al. Improved everyday executive function with Fintepla® (fenfluramine HCl oral solution): results from a phase 3 study in children and young adults with Dravet syndrome [abstract 2.454]. Presented at American Epilepsy Society annual meeting; November 30–December 4. New Orleans, LA; 2018.
13. Bishop KI, Isquith PK, Gioia GA, Gammaitoni AR, Farfel G, Galer BS, et al. 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. *Epilepsy Behav.* 2021;121(Pt A):108024.
14. Bishop KI, Isquith PK, Gioia GA, Knupp KG, Scheffer IE, Sullivan J, et al. FINTEPLA (fenfluramine) treatment improves everyday executive functioning in preschool children with Dravet syndrome: analysis from 2 pooled phase 3 clinical trials. Presented at American Epilepsy Society annual meeting; December 3–7, 2021. Chicago, IL.
15. Cross JH, Galer BS, Gil-Nagel A, Devinsky O, Ceulemans B, Lagae L, et al. Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome. *Seizure.* 2021;93:154–9.
16. Gioia GA, Isquith PK, Retzlaff PD, Espy KA. Confirmatory factor analysis of the behavior rating inventory of executive function (BRIEF) in a clinical sample. *Child Neuropsychol.* 2002;8(4):249–57.
17. Schoonjans AS, Marchau F, Paelinck BP, Lagae L, Gammaitoni A, Pringsheim M, et al. Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit-risk profile in a new patient population. *Curr Med Res Opin.* 2017;33(10):1773–81.
18. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30(4):303–71.
19. Sabaz M, Lawson JA, Cairns DR, Duchowny MS, Resnick TJ, Dean PM, et al. Validation of the quality of life in childhood epilepsy questionnaire in American epilepsy patients. *Epilepsy Behav.* 2003;4(6):680–91.
20. Varni JW, Seid M, Kurtin PS. PedsQL™ 4.0: reliability and validity of the pediatric quality of life inventory™ version 4.0 generic core scales in healthy and patient populations. *Med Care.* 2001;39(8):800–12.
21. Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet.* 2000;356(9242):1638–42.
22. Stiripentol (Diacomit): For Severe Myoclonic Epilepsy in Infancy (Dravet Syndrome). 2015; Available at: https://www.ncbi.nlm.nih.gov/books/NBK349347/pdf/Bookshelf_NBK349347.pdf. Accessed August 2, 2022.
23. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med.* 2017;376(21):2011–20.
24. Dmitrienko A, Tamhane AC. Gatekeeping procedures in clinical trials. In: Dmitrienko A, Tamhane AC, Bretz F, editors. *Multiple testing problems in pharmaceutical statistics*. Boca Raton, FL: Chapman and Hall/CRC; 2010. p. 165–91.
25. Ceulemans B, Schoonjans AS, Marchau F, Paelinck BP, Lagae L. Five-year extended follow-up status of 10 patients with Dravet syndrome treated with fenfluramine. *Epilepsia.* 2016;57(7):e129–34.
26. Schoonjans A, Paelinck BP, Marchau F, Gunning B, Gammaitoni A, Galer BS, et al. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. *Eur J Neurol.* 2017;24(2):309–14.
27. Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, et al. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. *Epilepsia.* 2012;53(7):1131–9.
28. Schoonjans AS, Ceulemans B. An old drug for a new indication: repurposing fenfluramine from an anorexigen to an antiepileptic drug. *Clin Pharmacol Ther.* 2019;106(5):929–32.
29. Guerrini R, Specchio N, Aledo-Serrano Á, Pringsheim M, Darra F, Mayer T, et al. An examination of the efficacy and safety of fenfluramine in adults, children, and adolescents with Dravet syndrome in a real-world practice setting: a report from the fenfluramine European early access program. *Epilepsia Open.* 2022;7(4):578–87.
30. Connolly HM, Cray JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, et al. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med.* 1997;337(9):581–8.
31. Agarwal A, Farfel GM, Gammaitoni AR, Wong PC, Pinto FJ, Galer BS. Long-term cardiovascular safety of fenfluramine in patients with Dravet syndrome treated for up to 3 years: findings from serial echocardiographic assessments. *Eur J Paediatr Neurol.* 2022;39:35–9.

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