A randomised, placebo-controlled trial of fenfluramine for the treatment of seizures in Dravet syndrome

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Research in context

Evidence before this study

PubMed was searched for any studies using the following search strategy: "(fenfluramine OR dexfenfluramine) AND (Dravet syndrome OR seizure* OR epilep*)." Case reports and small observational studies of the use of fenfluramine in children with intractable epilepsies, including photosensitive or self-induced, suggested that fenfluramine may possess anti-seizure activity. Two cohorts of patients with Dravet syndrome have been treated with low doses of fenfluramine for up to 30 years with significant sustained reductions in convulsive seizure frequency and without evidence of cardiovascular disease.

Added value of this study

This study was the first randomised, double-blind, placebo-controlled clinical trial to assess the safety and efficacy of fenfluramine when added to existing antiepileptic therapy for the treatment convulsive seizures associated with Dravet syndrome in children and young adults.

Implications of all the available evidence

The results of this randomised, placebo-controlled clinical trial suggest the use of low-dose fenfluramine (0·2 to ≤0·7 mg/kg/day [maximum daily dose of 26 mg/day]) added to existing antiepileptic therapy may be effective in reducing the frequency of convulsive seizures in patients with Dravet syndrome. The safety results indicate that patients treated with these doses of fenfluramine may experience an increase in adverse events, but overall the drug was well tolerated. Prospective echocardiographic examinations during the study revealed that

cardiac valve function remained within the normal physiologic range in all patients and none of the patients developed pulmonary arterial hypertension.

Summary

Background: Dravet syndrome is a rare, treatment-resistant developmental epileptic encephalopathy characterised by multiple types of frequent, disabling seizures. Fenfluramine has been reported to have antiseizure activity in observational studies of photosensitive epilepsy and Dravet syndrome. The aim of the present study was to assess the efficacy and safety of fenfluramine in patients with Dravet syndrome.

Methods: This randomised, double-blind, parallel group, placebo-controlled clinical trial enrolled children and young adults with Dravet syndrome. Following a 6-week observation period to establish baseline monthly (28 days) convulsive seizure frequency (MCSF; defined as hemiclonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs), patients were randomly assigned in a 1:1:1 ratio to placebo or fenfluramine 0·2 or 0·7 mg/kg/day, added to existing antiepileptic agents for 14 weeks. The primary outcome was the change in monthly frequency of convulsive seizures during the treatment period.

Findings: A total of 119 patients were enrolled, with mean age 9·0 years; 64 (54%) were male. No clinically relevant differences in baseline characteristics of patients in the three treatment groups were seen. During treatment, the median percent reductions in seizure frequency were -74·9% and -19·2% in the fenfluramine 0·7 mg/kg/day and placebo groups, respectively. The study met its primary efficacy endpoint with high statistical significance with fenfluramine 0·7 mg/kg/day demonstrating a -62·3% (P<0·0001, 95% CI: -47.7%, -72·8%) reduction in mean MCSF compared to placebo. The most common adverse events (≥10% of patients) occurring more frequently with fenfluramine were decreased appetite, diarrhoea, fatigue, lethargy, somnolence, and decreased weight. Echocardiographic examinations revealed valve function

within the normal physiologic range in all patients during the trial and no signs of pulmonary arterial hypertension.

Interpretation: In Dravet syndrome, fenfluramine provides significantly greater reduction in convulsive seizure frequency compared with placebo, while also exhibiting an apparent dose response, and is generally well tolerated. No valvular heart disease or pulmonary arterial hypertension was observed in any patient at any time.

Funding: Zogenix, Inc.

Trial registration numbers: NCT02682927, NCT02826863

Introduction

Dravet syndrome is a rare, treatment-resistant, developmental epileptic encephalopathy characterised by multiple types of frequent, disabling seizures and severe neurodevelopmental and psychomotor delay.[1,2] Current therapies remain inadequate for most patients; approximately 45% of patients have more than three tonic-clonic seizures per month despite multiple antiepileptic drugs, including stiripentol.[3] These patients also experience status epilepticus and increased mortality due to sudden unexpected death in epilepsy, for which generalised tonic-clonic seizures are a major risk factor.[4-7]

The antiepileptic activity of fenfluramine was reported in the 1980s in small case series and observational studies of children with photosensitive, self-induced epilepsy.[8] Fenfluramine, previously marketed for weight loss in obese adults, and often used in an off-label combination with phentermine, was withdrawn from the market in 1997 following the occurrence of cardiac valvulopathy[9] and pulmonary arterial hypertension[10] in some individuals treated with up to 220 mg/day.[9] Compassionate use approval was granted by the government of Belgium in 2002 to allow patients with Dravet syndrome to be treated with fenfluramine under a treatment protocol. Some of these patients have now been treated with daily fenfluramine for up to 30 years with sustained significant reductions in seizure frequency without evidence of cardiopulmonary disease.[11-13] The mean daily dosages reported as of the most recent visit in the two cohorts of Belgian patients were 0·27 mg/kg/day (range 0·13–0·46 mg/kg/day) and 0·35 (range, 0·16–0·69) mg/kg/day.[14] We report results from a Phase 3, randomised, placebo-controlled trial of fenfluramine HCl oral solution to treat seizures in children and young adults with Dravet syndrome.

Methods

Trial Design and Oversight

The sponsor (Zogenix, Inc., Emeryville, CA, USA) initiated two identical Phase 3 multinational, randomised, double-blind, placebo-controlled clinical trials of fenfluramine for the treatment of seizures in children and young adults with Dravet syndrome. One trial was conducted in the US and Canada (NCT02682927) and the other in Western Europe and Australia (NCT02826863). Due to incomplete enrolment in both studies of patients with this rare disorder, it was decided to merge the data sets prior to unblinding of results and analysis. The study protocols were reviewed and approved by the institutional review board or ethics committee for each study site before any study activation. All patients or their legal representatives signed informed consent/assent prior to enrolling in the trial.

Male or female patients aged 2 to 18 years with a medical history to support a clinical diagnosis of Dravet syndrome (**Supplementary Material**), and in whom seizures had not been completely controlled by their current regimen of antiepileptic drugs or other therapies, were eligible to enrol in the trial if they met inclusion and exclusion criteria. Patients were recruited from investigators' clinical practice populations, referrals, and advertising where permitted. Based on medical records or caregiver reports, patients must have had ≥4 convulsive seizures per four-week period during the 12 weeks prior to entering the screening/baseline period of the trial. Genetic testing was undertaken for all patients where permitted, but a positive *SCN1A* mutation was not required for enrolment. All medications or interventions for epilepsy must have been stable for at least four weeks before screening and were expected to remain stable throughout

trial participation. Key exclusion criteria prior to starting the screening/baseline period included a history of pulmonary hypertension; a history of cardiovascular or cerebrovascular disease, including aortic and/or mitral valve regurgitation as determined by echocardiographic examination, myocardial infarction, or stroke; current treatment with centrally-acting anorectic agents, monoamine oxidase inhibitors, or any centrally-acting agent with serotonin agonist or antagonist properties; treatment with stiripentol within 21 days prior to screening; a positive urine test for tetrahydrocannabinol; and a positive whole blood test for cannabidiol at screening. The Epilepsy Study Consortium (http://epilepsyconsortium.org/) confirmed that each patient met the diagnostic criteria for study entry.

Trial Procedures

Potential patients enrolled in a 6-week baseline period to establish seizure frequency and determine eligibility. Echocardiographic examinations were performed during the baseline period, and patients exhibiting aortic and/or mitral valve regurgitation of any severity were excluded from further participation. During the trial, seizures were documented by parents or caregivers in an electronic diary, including date, time of day, duration, and seizure type. To qualify for entry to the trial, each patient must have had ≥6 convulsive seizures during the baseline period with ≥2 in the first three weeks and ≥2 in the last three weeks. For this clinical trial, convulsive seizures were defined as hemiclonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs. At the end of the baseline period, eligible patients were randomly assigned in a 1:1:1 ratio to placebo, fenfluramine 0·2 mg/kg/day, or fenfluramine 0·7 mg/kg/day, with the maximum daily dose limited to 26 mg/day. Fenfluramine was administered as an oral solution of fenfluramine HCl containing 2.2 mg/mL

fenfluramine. Daily doses were administered orally with food in two equal doses—one in the morning and one in the evening, approximately 12 hours apart. During the first two weeks (titration period), patients in the fenfluramine 0·7 mg/kg/day group were blindly titrated to their final dose, starting with 0·2 mg/kg/day for four days, 0·4 mg/kg/day for four days, and then reaching the final dose. The other groups underwent dummy titrations. Following the titration period, patients were maintained on their final dose for an additional 12 weeks (maintenance period). At the conclusion of the treatment period (titration plus maintenance), eligible patients electing to continue in an optional open-label extension study (NCT02823145) underwent a blinded two-week transition period, whereas patients exiting the study underwent a two-week taper of medication and a safety follow-up.

Randomisation and Masking

Following the 6-week baseline period, eligible patients were randomised to treatment with placebo, fenfluramine 0·2 mg/kg/day, or fenfluramine 0·7 mg/kg/day. The assignment of treatment for each patient was done through an interactive web response system. The randomisation schedule was produced by an independent statistician and was stratified by age (<6 years, ≥6 years). The original protocol stated that each age group was to include at least 40% of enroled patients, but during the drafting of the statistical analysis plan (SAP) and after observing the age distribution of the study population of a recently completed study in Dravet syndrome,[15] the stratification regimen was changed in the SAP to achieve an age distribution of 25% in the <6 year old group. The fenfluramine and placebo solutions were identical in appearance and taste and thus indistinguishable from each other. Zogenix manufactured the

study drug and placebo. All patients, caregivers, investigators, and other persons involved in acquiring and assessing data were masked to treatment group assignment.

Safety

Adverse events were collected from the time of signing of informed consent until completion of the study, including the follow-up visit. Collection of adverse events occurred primarily at in-clinic or telephone study visits in discussion with the caregiver/parent. The severity of adverse events was graded by the investigator as mild, moderate, or severe, and related or not related to study medication. Vital signs, height, weight, and clinical laboratory evaluations were performed at each in-clinic study visit (during baseline, at randomization, and on study days 15, 43, 71, and 99). Since antiepileptic drug use has been associated with adverse effects on cognition, the Behavior Rating Inventory of Executive Function (BRIEF) or the BRIEF-P (for children age 2 to <5 years old)[16] was administered at baseline and after 7 and 14 weeks of treatment to determine if there were any negative effects of treatment on executive function, a construct of cognition. The instrument contains three index scores: the Behavioral Regulation Index, Metacognition Index, and Global Executive Composite. The Behavioral Regulation Index score represents a child's ability to shift cognitive set and modulate emotions and behaviour via appropriate inhibitory control, the Metacognition Index score represents a child’s ability to self-manage tasks, and the Global Executive Composite is a summary score that incorporates all eight clinical scales of the BRIEF. Higher scores represent increasing difficulty in executive function.

Conventional two-dimensional, spectral Doppler, and colour Doppler echocardiography and 12-lead electrocardiography were performed during the screening/baseline period, after six weeks of

treatment, and after 14 weeks of treatment at the end of the maintenance period. The echocardiograms were evaluated by two independent cardiologists, and in the event of disagreement, a third cardiologist arbitrated the decision. These three board-certified cardiologists were consultants of the cardiovascular clinical research organization, Biomedical Systems/ERT (St. Louis, MO), which served as the echocardiography and electrocardiogram core laboratory for this study. In addition, an International Paediatric Cardiology Advisory Board of experienced academic cardiologists with expertise in echocardiography was established to provide guidance and recommendations regarding cardiac assessments throughout the Phase 3 program. Cardiac valve regurgitation severity was graded as absent, trace, mild, moderate, or severe. Valvular heart disease (VHD) was defined as the presence of mitral valve regurgitation ≥ moderate severity and/or aortic valve regurgitation ≥ mild severity.[17] Pulmonary hypertension was considered to be present when pulmonary arterial systolic pressure (PASP) exceeded 35 mmHg.[18]

Outcomes

All primary, key-secondary, and other secondary outcomes were prespecified (with the exception of those labelled as post-hoc). Monthly convulsive seizure frequency (MCSF) was expressed per 28 days. The primary efficacy endpoint was the comparison of change in mean MCSF between the baseline period and the combined titration and maintenance periods in patients treated with fenfluramine 0·7 mg/kg/day compared with placebo. Five key secondary endpoints were prespecified: the comparison of the fenfluramine 0·2 mg/kg/day group with placebo for the change in mean MCSF between baseline and the combined titration and maintenance periods, comparison of both fenfluramine groups independently with placebo on the proportion of

patients who achieved a ≥50% reduction from baseline in mean MCSF, and comparison of both fenfluramine groups independently with placebo on the longest seizure-free interval observed in each group.

Other secondary outcomes included a responder analysis (i.e. the proportion of patients who achieved ≥25%, ≥75%, or 100% reduction in mean MCSF; the number of days that rescue medication was used during the treatment period; and a post-hoc analysis of patients who experienced zero or one convulsive seizure during the treatment period), a comparison of the Clinical Global Impression of Improvement assessed by the investigator and by the parent/caregiver, and patient quality of life assessments. The Clinical Global Impression of Improvement solicits a response on a 7-point Likert-like scale with responses ranging from 1 "very much improved" to 4 "no change" to 7 "very much worse."

The following instruments were used to assess patient quality of life: Quality of Life in Childhood Epilepsy Scale[19] and Pediatric Quality of Life Inventory.[20] The Quality of Life in Childhood Epilepsy Scale is a low-burden parent/caregiver-completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, well-being, cognition, social activities, behaviour, and general health. Its subscales and total score are expressed on a 0 to 100 scale, with higher values representing better quality of life. The Pediatric Quality of Life Inventory 4·0 is a quality of life scale that assesses four functional areas (Physical, Emotional, Social, and School Functioning). The scale is available in age-appropriate instruments with child self-report and parent proxy-report formats. In this clinical trial, the age-appropriate categories for the administration of the instrument were

ages 2-4, 5-7, 8-12, and 13-18 years; the parent reports were also used. Scores are expressed on a scale of 0 to 100, in which higher scores mean better health-related quality of life.

Statistical Analysis

The statistical analysis plan was written specifically for the merged clinical trial prior to completion of treatment and unblinding. The power analysis assumed that the standard deviation of the percentage change in monthly seizure frequency was 55%, based on results from previous randomised clinical studies of stiripentol[21,22] and cannabidiol[15] for the treatment of seizures in Dravet syndrome patients. Based on this assumption, a sample size of 40 patients per arm was determined to provide 90% power to detect a difference in mean change in monthly seizure frequency from baseline of 40 percentage points, using a two-sided test at the α=0·05 significance level.

The primary endpoint was analysed using an analysis of covariance (ANCOVA) model with treatment (three levels) and age group (<6 years, ≥6 years) as factors, log baseline convulsive seizure frequency as a covariate, and log convulsive seizure frequency during the combined titration and maintenance periods as the response. Inspection of residual plots and other diagnostics verified that the assumptions of the ANCOVA model were met with only minor deviations. Estimated treatment differences and CI endpoints were exponentiated to yield an estimate of the placebo-adjusted response. The comparison of fenfluramine 0·2 mg/kg/day with placebo for change in convulsive seizure frequency from baseline to the combined titration and maintenance periods was obtained from the same analysis. Treatment groups were compared on the proportion of patients who achieved a ≥50% reduction in convulsive seizure frequency using

a logistic regression model that incorporated the same factors as the primary endpoint analysis. The Wilcoxon rank sum test was used to compare groups on the longest seizure-free interval; the Hodges-Lehmann estimator was used to calculate 95% CIs on the median difference between groups. A serial gatekeeping procedure[23] was used to maintain the simultaneous type 1 error rate at $\alpha=0{\cdot}05$ across the analyses of the primary and five key secondary endpoints. No correction for multiplicity was performed for additional secondary endpoints. The primary and all key secondary endpoint analyses were performed on the modified intent-to-treat (mITT) population, defined as all patients who received at least one dose of study medication and had at least one week of post-treatment seizure diary data. These analyses were also conducted on the per-protocol population, which was defined as all patients who received at least 4 weeks of treatment in the maintenance period and who demonstrated a treatment compliance rate ≥80%. Missing data were not imputed.

The secondary responder analysis was assessed using logistic regression as described above. For the Clinical Global Impression of Improvement, the proportion of patients who were rated as "very much improved" or "much improved" in each fenfluramine dose group was compared to placebo using the Cochran-Mantel-Haenszel test stratified by age group. Comparisons between treatment groups for the quality of life assessments were made using Wilcoxon rank sum tests.

Role of the Funding Source

The study was funded by Zogenix, Inc., who designed the study with input from the investigators. Zogenix and the contracted clinical research organization (Syneos Health, Raleigh, NC, USA) were responsible for trial management, site monitoring, preparation of placebo and

active treatments, data monitoring, and statistical analysis. Zogenix paid for professional medical writing and editing assistance to the authors. All authors vouch for adherence to the protocol, accuracy of data collection and analysis, and reporting of adverse events. All authors had full access to all the data and were responsible for the decision to submit for publication. The corresponding author confirms having access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Patients

A total of 173 patients were screened for eligibility, with 119 patients enrolled and randomly assigned to a treatment group (**Figure 1**). Of the 54 screen failures, the two most common reasons were the presence of predefined exclusionary cardiovascular or cardiopulmonary findings, primarily trace mitral and/or trace aortic valve regurgitation during screening echocardiographic examination (n=23) and failure to meet other entry requirements (n=19). Nine patients withdrew before completion of the trial, three in the placebo group for lack of efficacy (n=1) or patient/guardian decision (n=2), and six in the fenfluramine 0·7 mg/kg/day group for adverse events (n=5) or patient/guardian decision (n=1). All patients reached the target dose; however, 6 subjects did not tolerate the 0·7 mg/kg/day dose as add-on therapy and either reduced the dose (n=3) or discontinued the trial (n=3). Upon completion of this clinical trial, 112 patients entered the open-label extension study.

Patient demographics are presented in **Table 1**. No clinically relevant differences in baseline characteristics of patients in the three treatment groups were seen. The average age of patients

was 9·0±4·7 years, and the baseline median convulsive seizure frequency per month ranged from 17·5 to 27·3 among the three treatment groups. Patients were being treated at baseline with a mean of 2·4±1·0 antiepileptic drugs (median, 2; range, 0 to 5), which most commonly included valproate (n=71, 60%), clobazam (n=70, 59%), topiramate (n=30, 25%), and levetiracetam (n=26, 22%). Fifty-eight (49%) patients had previously been treated with stiripentol, and 31 (26%) had previously been treated with cannabidiol. Overall mean compliance to study medication was >90% in each treatment group, as reported by caretakers in the daily diary and verified against returned medication. A total of 12 patients, all in the 0·7 mg/kg/day group, were treated with the maximum daily dose of 26 mg fenfluramine during the combined titration and maintenance periods.

Seizure Frequency

Seizure frequency during the 14-week treatment period declined by a median -74·9%, -42·3%, and -19·2% in the fenfluramine 0·7 mg/kg/day, and fenfluramine 0·2 mg/kg/day, and placebo groups, respectively (**Table 2**). The study met its primary efficacy endpoint with high statistical significance, with patients in the fenfluramine 0·7 mg/kg/day group demonstrating a 62·3% greater reduction in mean MCSF over the 14-week treatment period compared with placebo (P<0·0001, **Table 2**). The fenfluramine 0·2 mg/kg/day group also demonstrated a significant 32·4% reduction in mean MCSF compared with placebo (P=0·0209 **Table 2**). A significantly greater proportion of patients treated with either dose of fenfluramine demonstrated a ≥25%, ≥50%, or ≥75% reduction in MCSF during the treatment period compared with subjects in the placebo group (**Figure 2, Table 2**).

During the treatment period, 27 (68%; *P*<0·0001) and 15 (38%; *P*=0·0091) patients in the 0·7 mg/kg/day and 0·2 mg/kg/day fenfluramine groups, respectively, demonstrated a ≥50% reduction in convulsive seizure frequency compared with five (12%) patients in the placebo group (**Table 2, Figure 2**). The median longest seizure-free intervals were 25 days in the fenfluramine 0·7 mg/kg/day group (*P*<0·0001), 15 days in the fenfluramine 0·2 mg/kg/day group (*P*=0·0352), and 9.5 days in the placebo group (**Table 2**). Seizure freedom during the entire 14-week treatment period was experienced by three (8%) patients in the fenfluramine 0·7 mg/kg/day group, three (8%) patients in the fenfluramine 0·2 mg/kg/kg group, and 0 patients in the placebo group, and only one seizure was reported in the entire 14-week treatment period by seven (18%) in the 0·7 mg/kg/day group, two (5%) in the 0·2 mg/kg/day group, and 0 patients in the placebo group (**Table 2**). In addition to its antiseizure activity, patients in the 0·7 mg/kg/day treatment group required significantly fewer days of rescue medication use (**Table 2**).The per-protocol population comprised 103 patients and analyses of the primary and key secondary endpoints in this patient population yielded similar results to the analyses of the mITT population.

During the trial, 68 of 119 (57%) patients experienced other seizure types, including focal seizures without clearly observable motor signs and absence or atypical absence, myoclonic, or atonic seizures. Patients treated with fenfluramine 0·7 mg/kg/day demonstrated a median 68·3% decrease from baseline in total seizure frequency compared with median decreases of 41·1% and 16·2% in the fenfluramine 0·2 mg/kg/day and placebo groups, respectively (**Table 2**).

At the end of the treatment period, 22 (55%; *P*<0·0001) patients in the fenfluramine 0·7 mg/kg/day group and 16 (41%; *P*=0·0036) patients in the fenfluramine 0·2 mg/kg/day group were rated as "much improved" or "very much improved" by their caretaker, compared with four (10%) patients in the placebo group (**Table 2**). The numbers of patients rated "much improved" or "very much improved" by the investigator were 25 (62%; *P*<0·0001), 16 (41%; *P*=0·0032), and four (10%) in the fenfluramine 0·7 mg/kg/day, fenfluramine 0·2 mg/kg/day, and placebo groups, respectively (**Table 2**).

No significant differences were observed after 14 weeks of treatment between either fenfluramine group and placebo in the overall composite score from the Quality of Life in Childhood Epilepsy instrument (**Table 2**); however, significant differences were observed in the Pediatric Quality of Life Inventory. At baseline the mean parent-reported Pediatric Quality of Life Inventory total scores were 48·7±18·1, 49·5±11·9, and 45·6±17·1 in the fenfluramine 0·7 mg/kg/day, fenfluramine 0·2 mg/kg/day, and placebo groups, respectively. At the end of the treatment period, total scores had improved by means of 5·9±15·1 and 6·8±11·2 in the fenfluramine 0·7 mg/kg/day (*P*=0·0198) and fenfluramine 0·2 mg/kg/day (*P*=0·0029) groups, respectively, compared with a small decrease or worsening in the placebo group (-1·6±10·4) (**Table 2**).

Post-hoc analyses of treatment effect can be found in the Supplementary Material, including achieving a state of near-seizure freedom (defined as experiencing 0 or 1 convulsive seizure during the 14-week treatment period) and the time course of antiseizure activity.

Safety

Adverse events were reported in 65% of patients in the placebo group and 95% of patients in each fenfluramine dose group. A summary of non-cardiovascular adverse events that occurred in ≥10% of patients in any treatment group is presented in **Table 3**. The most common non-cardiovascular adverse events reported in fenfluramine-treated patients were decreased appetite, diarrhoea, nasopharyngitis, lethargy, somnolence, and pyrexia. Among patients that had non-cardiovascular adverse events, 93% were mild to moderate in severity, including 35 (92%), 35 (95%), and 24 (92%) of patients in the fenfluramine 0·7 mg/kg/day, fenfluramine 0·2 mg/kg/day, and placebo groups, respectively.

Because fenfluramine had been marketed at higher doses as an anorectic drug, body weight was monitored throughout the trial. Median changes in body weight by age group and treatment are presented in **Table 2**. Furthermore, a change from baseline ≥7% was set as the minimum threshold for identifying meaningful weight loss. Overall, in the placebo group, one (3%) patient lost weight (maximum 8·0% at Visit 8). In the fenfluramine 0·2 mg/kg/day group, five (13%) patients experienced weight losses ranging from 8·4% to 21·9% of body weight; the patient who lost 21·9% of body weight was being actively managed for obesity by a nutritionist to lose excess body weight before and during the trial. In the fenfluramine 0·7 mg/kg/day group, 8 (20%) patients lost weight, ranging from 7·2% to 11·4% of body weight. One patient in the fenfluramine 0·7 mg/kg/day group discontinued, citing decreased appetite and weight loss (which was less than 1 kg), among other events.

No deaths occurred in the trial. Serious adverse events occurred in four (10%) patients in the placebo group, four (10%) patients in the fenfluramine 0·2 mg/kg/day group, and five (13%) patients in the fenfluramine 0·7 mg/kg/day group. The most common serious adverse events included hospitalization for status epilepticus in two (5%) placebo patients, one (3%) fenfluramine 0·2 mg/kg/day patient, and two (5%) fenfluramine 0·7 mg/kg/day patients.

No cases of pulmonary arterial hypertension or clinically significant signs or symptoms of cardiovascular disease were observed in the trial. All echocardiographic examinations revealed valvular function within the normal physiological range in all patients throughout the trial. Five (13%), seven (18%), and nine (23%) patients in the placebo, fenfluramine 0·2 mg/kg/day, and fenfluramine 0·7 mg/kg/day groups, respectively, were noted to have at least one echocardiographic finding with trace mitral and/or trace aortic regurgitation, which is considered to be a physiologic and normal finding seen in healthy children and young adults.[24]

After 14 weeks of treatment, patients in the fenfluramine 0·7 mg/kg/day group demonstrated significant improvements from baseline in the BRIEF Behavioral Regulatory Index and Global Executive Composite score (**Table 2**).

Discussion

Dravet syndrome is a severe refractory, disabling childhood-onset developmental epileptic encephalopathy characterised by a high seizure burden accompanied by significant comorbid neurodevelopmental, motor, and behavioural abnormalities.[2] In addition, the syndrome is marked by high mortality, most frequently due to status epilepticus and sudden unexpected death in

epilepsy.[5] A Dravet-specific SUDEP rate of 9·32 per 1000 person-years has been reported,[5] which is substantially higher than that reported in the general population of patients with epilepsy.[6] Despite the use of multidrug regimens used in an attempt to control seizures, 45% continue to experience ≥4 tonic-clonic seizures/month.[3] The combination of a high seizure burden and neurodevelopmental abnormalities imparts a high humanistic and economic impact on caregivers and the broader family unit.[2,25,26] Primary caregivers have reported general health scores on the EQ-5D that are equivalent to someone in the general population suffering from a major health illness (i.e. heart disease, diabetes, cancer).[25] These reports illustrate the high unmet need for new and better therapies in Dravet syndrome.

In this clinical trial, fenfluramine oral solution resulted in a robust reduction in the frequency of convulsive seizures compared with placebo in children and young adults with Dravet syndrome. In addition, significantly higher responder rates compared with placebo, particularly of patients demonstrating both ≥50% and ≥75% reduction in the frequency of convulsive seizures, were observed. The cohort of patients with Dravet syndrome included in the current trial reflect the high seizure burden previously described in that they were averaging about 1·5 convulsive seizures/day (baseline convulsive seizure frequency/28 days = 40·3±64·0 [mean±SD]). On this background of high seizure burden, further illustration of the efficacy of fenfluramine can be found in the fact that ten (25%) and five (13%) of patients in the 0·7 mg/kg/day and 0·2 mg/kg/day groups, respectively, had either one or no convulsive seizures for the entire 14-week study. Both the investigators and the parents/caregivers rated a significantly larger proportion of fenfluramine-treated patients as being “much improved” or “very much improved”

compared with patients in the placebo group. In the primary and all key secondary efficacy outcomes, a dose response was observed for the two fenfluramine doses studied.

Improvements on some, but not all, quality of life measures were seen at the end of 14 weeks of treatment with fenfluramine compared with placebo. No effect was seen in the Quality of Life in Childhood Epilepsy instrument, but the Pediatric Quality of Life Inventory showed improvement in both fenfluramine groups compared with placebo. The BRIEF assesses executive function, a construct of cognition, and was included as a safety measure to assess if treatment resulted in any negative effects on cognitive function, as this outcome has previously been reported with other antiepileptic medications.[27] The results showed this was not the case with fenfluramine, but rather, improvements in the BRIEF Behavioral Regulation Index, Metacognition Index, and Global Executive Composite scores were noted, while scores from the placebo group worsened on all three indexes. Current understanding suggests that both seizure burden and neuronal sodium channel dysfunction caused by *SCN1A* mutations may contribute to cognitive dysfunction in Dravet syndrome patients,[28,29] and reports exist suggesting that effective seizure control, even in adults, can result in improvement in cognitive abilities.[29] In addition to the significant reductions in seizure frequency noted with fenfluramine in the current study, a direct action of the medication on cognitive function cannot be ruled out. Further analyses of the full Phase 3 patient population, including the long-term longitudinal assessment from the safety extension study, will be required to fully characterise the potential for fenfluramine to impact non-seizure endpoints, such as quality of life and executive function.

The safety and adverse events of fenfluramine with respect to non-cardiovascular events were similar to what has been previously reported for fenfluramine from the Belgian cohorts with Dravet syndrome,[11-13] with lethargy and decreases in appetite being reported more commonly in patients treated with fenfluramine than with placebo. Fenfluramine was previously marketed as an appetite suppressant, and 21% to 38% of patients in the active treatment groups experienced decreases in appetite; weight loss above the 7% threshold was observed in 13% and 20% of patients in the fenfluramine 0·2 and 0·7 mg/kg/day groups, respectively. Serious adverse events occurred with similar frequency across all three treatment groups.

Cardiovascular safety is an important outcome measure in the evaluation of the use of fenfluramine to treat patients with Dravet syndrome.[9] Based on reports of cardiac valve disease in adult obese patients treated with up to 220 mg/day, fenfluramine was withdrawn from worldwide markets beginning in 1997.[30] Both increasing dose and increasing duration of treatment have been reported as risk factors for valvulopathy when fenfluramine was used as a weight loss agent in obese adult patients. Li and colleagues examined the records of the patients in the original FDA report[17] and found that the risk of severe valvulopathy was increased 9.2-fold (95% CI: 2.1, 40.8) in patients treated with ≥60 mg/day compared with patients treated with <40 mg/day.[31] Others have identified three and six months of use of fenfluramine as a threshold for increased risk of valvulopathy[32] and pulmonary arterial hypertension,[33] respectively.[32,34,35] In the present trial, all patients were treated with ≤30 mg/day of fenfluramine and were monitored with colour Doppler echocardiographic examinations before and during the trial to identify functional changes in cardiac valves and signs of pulmonary hypertension. During the 14-week treatment period and the two-week transition period at the end of the maintenance period, all

echocardiographic examinations revealed valve function within the normal physiologic range, and no pulmonary arterial hypertension was observed in any patient at any time. Not unexpectedly, a total of 21 patients, including five patients in the placebo group, had at least one echocardiographic finding with trace mitral and/or trace aortic regurgitation during the trial. Trace regurgitation is not considered evidence of valve dysfunction; rather, it is described in current guidelines as a physiologic finding seen in normal healthy children and adults.[24,36,37] Although the observations in the current study suggest a dose response for the finding of trace regurgitation, continued treatment in the long-term extension of this study showed a disappearance of this association. None of these patients, or any other patient enrolled in the open-label extension study of fenfluramine in patients with Dravet syndrome has demonstrated any grade of valvular regurgitation greater than trace during a median 256 days of observation.[38] The point prevalence of trace mitral valve regurgitation in the extension study was ≤11% at any time point, and for nearly all patients this finding was transient or fluctuating between trace and absent in subsequent echocardiographic examinations. Although the prevalence of trace regurgitation in young patients with Dravet syndrome is not known, 23 of 173 (13%) patients who were screened for participation in the present trial were excluded due to trace mitral regurgitation on screening echocardiographic examination. This prevalence is similar to that reported in healthy school-age children. Webb et al. reported a cross-sectional prevalence of trace/physiologic mitral regurgitation of 15% (n=59) in a group of 396 school-age children.[39]

Importantly, the conclusions about the cardiovascular safety of fenfluramine are limited by the relatively short treatment and observation period of 14 weeks in this trial. These findings are consistent with those reported with long-term use of fenfluramine at doses between 0·13-0·69

mg/kg/day in Dravet syndrome in Belgium,[8] where no cases of valve dysfunction or pulmonary hypertension have been reported with up to 30 years of dosing with ongoing echocardiographic examinations.

Although the trial employed a double-blind design, one potential limitation is the occurrence of side effects, especially ones known to be associated with the active treatment, that might cause a patient or caregiver to suspect having received the active treatment and therefore affect the reporting of seizures. In this trial, the most common side effect among fenfluramine-treated patients was decreased appetite, which occurred in 13 (38%) patients in the 0·7 mg/kg/day dose group.

In conclusion, this randomised controlled clinical trial demonstrated that fenfluramine significantly reduced the frequency of convulsive seizures in children and young adults with Dravet syndrome when added to existing antiepileptic treatment; while also exhibiting an apparent dose response effect. Fenfluramine was associated with decreased appetite, diarrhoea, lethargy, and somnolence, without the development of any cardiovascular adverse events. Further study is warranted to confirm long-term efficacy and safety, including the effect on cardiac valves, when fenfluramine is used for the treatment of Dravet syndrome.

Acknowledgments

The trial was funded by Zogenix, Inc., who designed the study with input from the investigators. The sponsor and the contracted clinical research organization were responsible for trial management, site monitoring, preparation of placebo and active treatment, data monitoring and

statistical analysis. The authors received professional medical writing and editing assistance from Edward Weselcouch, PhD, and Diana Talag, ELS, of PharmaWrite, LLC, in Princeton, NJ, and funded by Zogenix, Inc. The authors thank Dr. Susan Cheng for her important insights on the interpretation of echocardiographic findings.

Finally, the authors also thank the **F**enfluramine **A**ssessment **i**n **R**are **E**pilepsy (FAiRE) DS Investigators:

Australia: Deepak Gill, MBBS, Kate Riney, MBBCh, Ingrid Scheffer, MBBS; **Belgium:** Berten Ceulemans, MD; **Canada:** Jeffrey Buchhalter, MD, Lionel Carmant, MD, Mary Connolly, MBBCh; **Denmark:** Marina Nikanorova, MD; **France:** Rima Nabbout, MD; **Germany:** Ulrich Brandl, MD, Julia Jacobs-LeVan, MD, Thomas Mayer, MD, Axel Panzer, MD, Tilman Polster, MD, Milka Pringsheim, MD, Ulrich Stephani, MD, Markus Wolff, MD; **Italy:** Domenica Battaglia, MD, Francesca Beccaria, MD, Francesca Darra, MD, Tiziana Granata, MD, Renzo Guerrini, MD, Antonio Romeo, MD, Pasquale Striano, MD, Federico Vigevano, MD; **Spain:** Antonio Gil-Nagel, MD, Victoria San Antonio, MD, Rocio Sanchez-Carpintero, MD; **United Kingdom:** J. Helen Cross, MBChB, Archana Desurkar, MD, Elaine Hughes, MD, Anand Iyer, MD, Sunny Philip, MD, Sameer Zuberi, MD; **United States:** Gregory Sharp, MD, Frank Berenson, MD, Orrin Devinsky, MD, Kelly Knupp, MD, Linda Laux, MD, Eric Marsh, MD, Mark Nespeca, MD, Ian Miller, MD, Robert Nahouraii, MD, Juliann Paolicchi, MD, Steven Phillips, MD, Michael Scott Perry, MD, Annapurna Poduri, MD, Ben Renfroe, MD, Russell Saneto, DO, Asim Shahid, MD, Douglas Smith, MD, Marcio Sotero de Menezes, MD, Joseph Sullivan, MD, Matthew Sweney, MD, Dinesh Talwar, MD, Elizabeth Thiele, MD, James Wheless, MD, Angus Wilfong, MD, Elaine Wirrell, MD, Mary Zupanc, MD.

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Data collection: LLagae, JS, KK, LLaux, TP, MN, OD, JHC, RG, DT, IM, BC

Data analysis: ML

Data interpretation: All authors contributed equally to the interpretation of the efficacy and non-cardiovascular safety findings. In addition, WWL and AA provided the primary interpretation of the cardiovascular safety findings.

Writing: The authors participated in a preliminary conference to discuss the structure and focus of the manuscript. An outline based on this conference was prepared by AG, LLagae, BC, and JS and was reviewed by all authors. The primary writers of the manuscript were GF, BSG, AG, LLagae, JS, ML, and BC. All authors contributed equally to the review and revision of the manuscript, and all author approved the final version.

Role of Medical Writer and Editor

Edward Weselcouch, PhD (PharmaWrite, LLC, Princeton, NJ) provided professional medical writing assistance to the authors. Diana Talag, ELS (PharmaWrite, LLC, Princeton, NJ) provided professional editorial assistance and submission assistance to the authors. This assistance was funded by Zogenix, Inc.

Declaration of Interests

- L. Lagae: Received grants, personal fees, and other as a consultant/speaker from Zogenix during the conduct of the study; other as a consultant/speaker from LivaNova, grants and

other as a consultant/speaker from UCB, other as a speaker from Shire, and other as a speaker from Eisai outside the submitted work. Dr. Lagae has a patent for ZX008 for the treatment of Dravet syndrome and infantile epilepsies assigned to his institution and licensed to Zogenix.

- JS: Received grants and travel support as an investigator from Zogenix, other as an advisory board member from the Dravet Syndrome Foundation, personal fees as a reviewer from the Epilepsy Study Consortium, and serves as a consultant for Epygenix during the conduct of the study.
- KK: Received research grants from Zogenix and grants from the Pediatric Epilepsy Research Foundation during the conduct of the study; grants from the Colorado Department of Public Health, grants from West Therapeutics, and other as a DSMB member from Greenwich Pharmaceuticals outside the submitted work.
- L. Laux: Received grants as primary investigator from Zogenix during the conduct of the study and grants as primary investigator from GW Pharma outside the submitted work.
- TP: Received personal fees from Zogenix during the conduct of the study and personal fees from Desitin, Shire, Novartis, and UCB outside the submitted work.
- MN: Received institutional grants from Zogenix during the conduct of the study.
- OD: Received research grants from Zogenix during the conduct of the study and received research grants from Novartis and PTC Therapeutics and has equity interest in Rettco, Pairnomix, Tilray, and Egg Rock Holdings outside the submitted work.
- JHC: Received institutional research grants from Zogenix during the conduct of the study and received institutional research grants and other as an investigator, speaker, and advisor from GW Pharma, other as a speaker/advisor from Shire, other as an

advisor/speaker from Zogenix, other as speaker from Biomarin, and other as advisor from Eisai outside the submitted work.

- RG: Received research grants from Zogenix during the conduct of the study and received personal fees as a speaker/consultant from Zogenix outside the submitted work.
- DT: Received grants from Zogenix during the conduct of the study and received personal fees from Sunovion and Eisai outside the submitted work.
- IM: Received grants and personal fees (honoraria, travel support) from Zogenix during the conduct of the study and received grants and personal fees (honoraria, travel support) from GW Pharmaceuticals, INSYS Therapeutics, Dravet Syndrome Foundation, Greenwich, INSYS, Neurelis, NeuroPace, Tuberous Sclerosis Alliance, Ultragenyx, and Visualase outside the submitted work.
- GF, BSG, AG, AM, GM, AA: Received personal fees and own stock as employees from Zogenix.
- ML: Received personal fees as a consultant from Zogenix during the conduct of the study and received personal fees as a consultant from Zogenix outside the submitted work.
- WWL: Received personal fees and non-financial support from Zogenix during the conduct of the study.
- BC: Received grants from Zogenix during the conduct of the study and has a patent for ZX008 for the treatment of Dravet syndrome and infantile epilepsies assigned to his institution and licensed to Zogenix.
- LL, BC, and the 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 the KU Leuven University/Antwerp University Hospital.

Role of the Funding Source

The study was funded by Zogenix, Inc., who designed the study with input from the investigators. Zogenix and the contracted clinical research organization (Syneos Health, Raleigh, NC, USA) were responsible for trial management, site monitoring, preparation of placebo and active treatments, data monitoring, and statistical analysis. Zogenix paid for professional medical writing and editing assistance to the authors. All authors vouch for adherence to the protocol, accuracy of data collection and analysis, and reporting of adverse events. All authors had full access to all the data and were responsible for the decision to submit for publication. The corresponding author confirms having access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics Committee Approval

The study protocols were reviewed and approved by the institutional review board or ethics committee for each study site before any study activation. All patients or their legal representatives signed informed consent/assent prior to enrolling in the trial.

Data Sharing Statement

Zogenix, Inc. does not currently have a data sharing policy.

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763 **Table 1.** Demographics and Baseline Convulsive Seizure Frequency

	Fenfluramine 0·7 mg/kg/day	**Fenfluramine 0·2 mg/kg/day**	**Placebo**	**Overall**
n	40	39	40	119
Age, years				
Mean±SD (min, max)	8·8±4·4 (2, 18)	9·0±4·5 (2, 17)	9·2±5·1 (2, 18)	9·0±4·7 (2, 18)
Age group <6 years, n (%)	11 (28)	9 (23)	11 (28)	31 (26)
Males, n (%)	21 (52)	22 (56)	21 (52)	64 (54)
Race, n (%)				
Caucasian	34 (85)	33 (85)	31 (78)	98 (82)
Asian	1 (3)	2 (5)	4 (10)	7 (6)
Other or not reported*	5 (12)	4 (10)	5 (12)	14 (12)
Body weight, kg				
Mean±SD	31·8±13·5	35·1±19·6	31·7±16·2	32·9±16·5
BMI, kg/m^2				
Mean±SD	18·5±3·5	19·3±5·7	18·0±3·8	18·6±4·4
SCN1A mutations, n (%)	33 (82)	31 (80)	31 (78)	95 (80)
Geographic region, n (%)				
United States and Canada	24 (60)	24 (61)	24 (60)	72 (60)
Rest of world	16 (40)	15 (39)	16 (40)	47 (40)
Number of concomitant antiepileptic drugs				
Mean±SD	2·3±0·9	2·5±1·1	2·5±0·9	2·4±1·0

	Fenfluramine 0·7 mg/kg/day	**Fenfluramine 0·2 mg/kg/day**	**Placebo**	**Overall**
Concomitant antiepileptic drugs, n (%)				
Valproate (all forms)	25 (62)	24 (62)	22 (55)	71 (60)
Clobazam	24 (60)	24 (62)	22 (55)	70 (59)
Topiramate	11 (28)	10 (26)	9 (22)	30 (25)
Levetiracetam	4 (10)	11 (28)	11 (28)	26 (22)
Patients treated with maximum dose of fenfluramine (26 mg/day) n (%)	12 (30)	0 (0)	0 (0)	12 (10)
Baseline convulsive seizure frequency per 28 days				
Mean±SD	31·4±30·6	45·5±99·8	44·2±40·2	40·3±64·0
(median)	(20·7)	(17·5)	(27·3)	(24·1)
[range]	[4·8, 124]	[4·7, 623·5]	[3·3, 147·3]	[3·3, 623·5]

764 *Privacy laws in some regions preclude disclosure of certain personal information.

765 **Table 2.** Efficacy Endpoints

	Fenfluramine 0·7 mg/kg/day (n=40)	**Fenfluramine 0·2 mg/kg/day (n=39)**	**Placebo (n=40)**
Primary and key secondary endpoints[*]			
Change in convulsive seizure frequency per 28 days			
Estimate of % difference from placebo[†]	-62·3 (-47·7, -72·8)[‡]	-32·4 (-6·2, -51·3)[§]	
P value	*P*<0·0001	*P*=0·0209	
Responder analysis: ≥50% reduction in convulsive seizure frequency			
n (%)	27 (68)[§]	15 (38)[§]	5 (12)
P value	*P*<0·0001	*P*=0·0091	
Odds ratio (95% CI)) [a]	15·0 (4·5, 50)	4·8 (1·5, 15)	
Longest seizure-free interval, days			
Mean±SD	32·9±27·5	26·0±31·7	10·6±6·0
Median (range)	25·0 (2, 97)[§]	15 (3, 106)[§]	9·5 (2, 23)
Estimate of median treatment difference (95% CI)	15·5 (6, 25)	4·5 (0, 9)	
P value	*P*=0·0001	*P*=0·0352	

Other secondary endpoints‖			
≥25% reduction in convulsive seizure frequency, n (%)	36 (90)	26 (67)	14 (35)
P value	*P*<0·0001	*P*=0·0041	
Odds ratio (95% CI)) [a]	22·3 (6, 84)	4·1 (2, 11)	
≥75% reduction in convulsive seizure frequency, n (%)	20 (50)	9 (23)	1 (2)
P value	*P*=0·0005	*P*=0·0229	
Odds ratio (95% CI) [a]	55·1 (6, 526)	12·0 (1·4, 102)	
100% reduction in convulsive seizure frequency, n (%)¶	3 (8)	3 (8)	0 (0)
Days of rescue medication use per 28 days during treatment			
Mean±SD	0·9±1·9	1·7±2·9	3·1±4·6
Median (min, max)	0 (0, 8)	0·3 (0, 16)	1·7 (0, 24)
P value	*P*<0·0001	*P*=0·0822	
Convulsive seizure frequency per 28 days, median (range)			
Percent change from baseline	-74·9 (-100, 196·4)	-42·3 (-100, 197·6)	-19·2 (-76·1, 51·8)
P value	*P*<0·0001	*P*=0·2035	
Total seizure frequency per 28 days, median (range)			
Percent change from baseline	-68·3 (-100, 35·6)	-41·1 (-100, 292)	-16·2 (-77·6, 601)
P value	*P*<0·0001	*P*=0·0202	

Other· seizure frequency per 28 days, median (range)			
Number of patients experiencing other seizure types	24	23	21
Percent change from baseline	-76·0 (-100, 69·2)	-50·6 (-100, 534)	-55·6 (-100, 723·6)
P value	*P*=0·0458	*P*=0·7585	
Non-seizure outcomes			
Change in body weight, kg; median (range; n)			
Age group			
2-4 years	0.4 (-1.5, 1.1; n=7)	-0.1 (-1.6, 0.7; n=8)	1.1 (-0.2, 1.4; n=9)
5-12 years	-0.9 (-5.9, 0.8; n=23)	0.3 (-9.0, 3.7; n=21)	1.0 (-1.1, 3.6; n=19)
13-18 years	-2.6 (-4.5, 1.6; n=8)	-0.4 (-9.8, 3.4; n=10)	0.2 (-0.6, 7.6; n=11)
Clinical Global Impression of Improvement			
Parent/caregiver rating, n (%)			
"Very much improved" or "Much improved"	22 (55)	16 (41)	4 (10)
P value	*P*<0·0001	*P*=0·0036	
Investigator rating, n (%)			
"Very much improved" or "Much improved"	25 (62)	16 (41)	4 (10)
P value	*P*<0·0001	*P*=0·0032	

Quality of Life in Childhood Epilepsy – Overall Quality of Life[††]			
Baseline, mean±SD	38·4±12·8	42·4±12·3	34·6±10·4
Change from baseline, mean±SD	5·8±11·7	0·8±11·8	1·5±8·7
P value	*P*=0·2807	*P*=0·3683	
Quality of Life, Pediatric Quality of Life Inventory Total Score [††]			
Baseline, mean±SD	48·7±18·1	49·5±11·9	45·6±17·1
Change from baseline, mean±SD	5·9±15·1	6·8±11·2	-1·6±10·4
P value	*P*=0·0198	*P*=0·0029	
Executive Function, Behavioral Rating Inventory of Executive Function (BRIEF) [‡‡ §§]			
Behavioral Regulation Index			
Baseline, mean±SD	75·1±18·3	74·4±16·4	73·7±18·1
Change from baseline, mean±SD (95% CI)	-4·4±10·5 (-8·34, -0·52)	-3·4±8·6 (-6·82, 0·01)	3·0±8·7 (-0·54, 6·62)
P value	*P*=0·0117	*P*=0·0185	
Metacognition Index			
Baseline, mean±SD	106·3±25·0	104·0±23·9	103·7±25·1

Change from baseline, mean±SD (95% CI)	-6·6±20·7 (-14·32, 1·12)	-1·0±16·4 (-7·51, 5·44)	5·9±19·1 (-2·02,13·78)
P value	*P*=0·0925	*P*=0·1994	
Global Executive Composite			
Baseline, mean±SD	181·4±40·9	178·4±37·7	177·4±40·2
Change from baseline, mean±SD	-11·0±29·1	-4·4±22·3	8·9±24·9
(95% CI)	(-21·91, -0·15)	(-13·27, 4·38)	(-1·35, 19·19)
P value	*P*=0·0245	*P*=0·0669	

[*] A hierarchal gatekeeping procedure was used to maintain the simultaneous type 1 error rate at α=0·05 across the analyses of the primary and five key secondary endpoints.

[†] Results are based on an analysis of covariance model with treatment group (3 levels) and age group (<6 years, ≥6 years) as factors, log baseline convulsive seizure frequency as a covariate, and log convulsive seizure frequency during the treatment period (titration + maintenance) as response. The *P* values were obtained from this model.

‡ Primary outcome.

[§] Key secondary outcome analysis.

‖ No correction for multiple comparisons was employed for other secondary outcomes.

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

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

[††] Increases in total score indicate improvement.

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

[§§] Negative scores indicate an improvement.

[a] Odds ratios (ORs) are for comparison with placebo. An age-adjusted logistic regression model was used to estimate all ORs except for those comparing fenfluramine 0·7 mg/kg/day to placebo at the 25% and 75% responder levels. The age adjustment was eliminated from those two comparisons due to potential instability in the model. Note that an OR >1 can be much larger than the corresponding relative risk. For example, in the comparison of fenfluramine 0·7 mg/kg/day to placebo at the 75% responder level, the OR was 39·0 whereas the relative risk was 20.

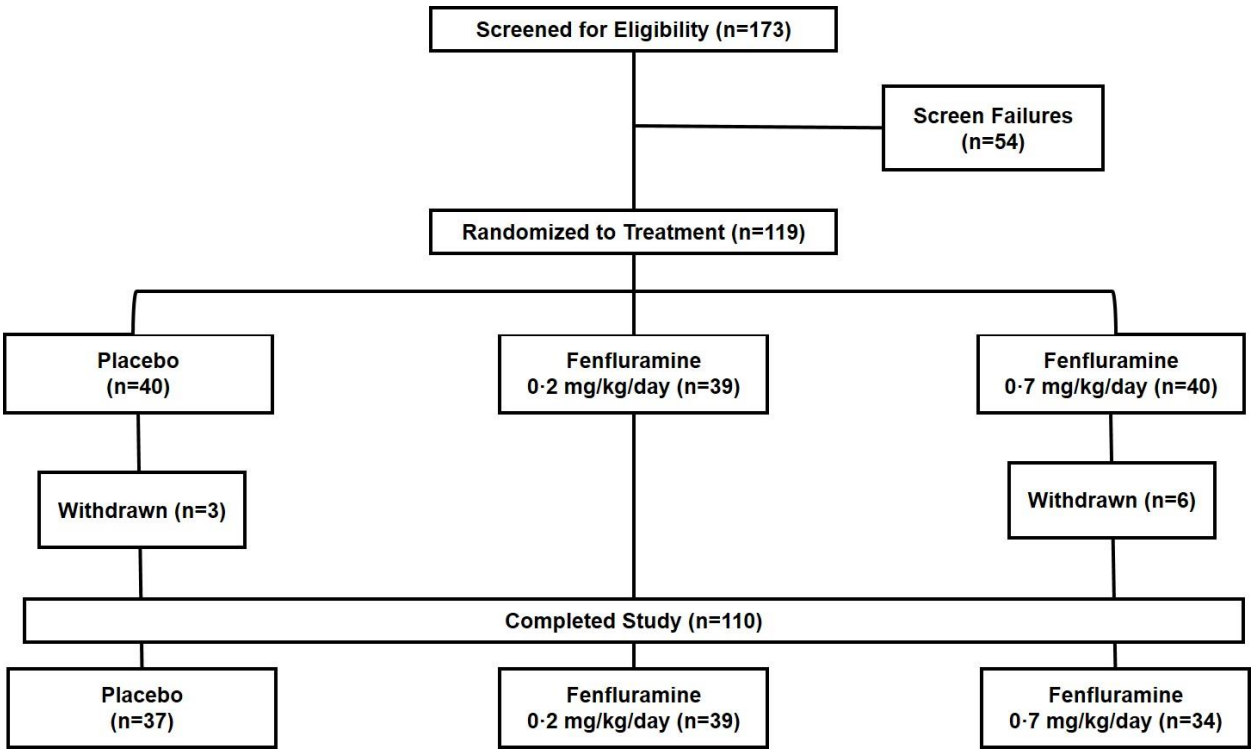
783 **Table 3.** Non-cardiovascular Adverse Events Occurring in ≥10% of Patients in Any Treatment

784 Group

	Placebo (n=40)	**Fenfluramine 0·2 mg/kg/day (n=39)**	**Fenfluramine 0·7 mg/kg/day (n=40)**
Patients with ≥1 adverse event, n (%)	26 (65)	37 (95)	38 (95)
Decreased appetite	2 (5)	8 (20)	15 (38)
Diarrhoea	3 (8)	12 (31)	7 (18)
Fall	2 (5)	4 (10)	0 (0·0)
Fatigue	1 (2)	4 (10)	4 (10)
Lethargy	2 (5)	4 (10)	7 (18)
Nasopharyngitis	5 (12)	4 (10)	7 (18)
Pyrexia	8 (20)	7 (18)	2 (5)
Seizure	5 (12)	4 (10)	3 (8)
Somnolence	3 (8)	6 (15)	4 (10)
Upper respiratory tract infection	5 (12)	8 (21)	0 (0·0)
Vomiting	4 (10)	4 (10)	3 (8)
Weight decreased	0 (0)	5 (13)	2 (5)

785

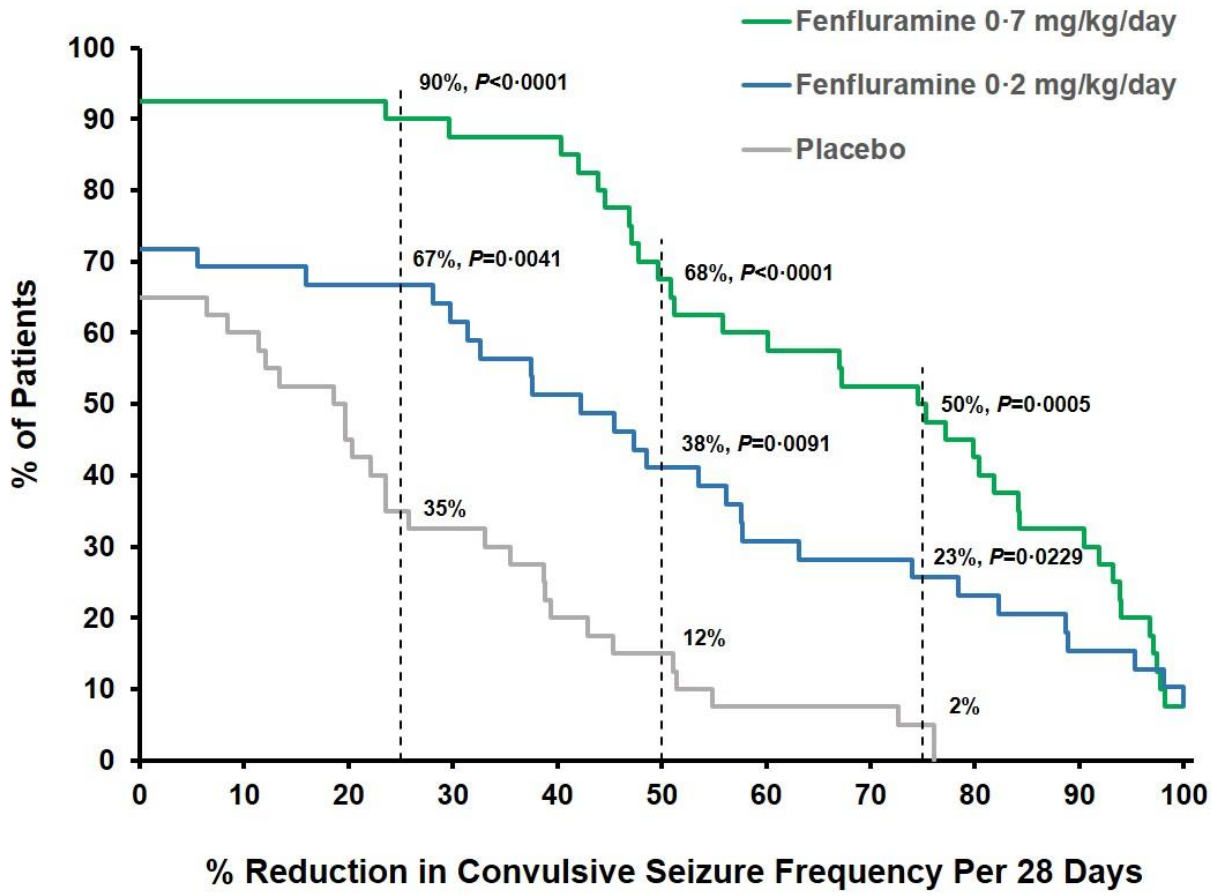
Figure 1. CONSORT diagram.



Patient enrolment started on 15 January 2016 and the final study visit occurred on 14 August 2017. The adverse events cited as reasons for early withdrawal in the fenfluramine 0·7 mg/kg/day group included: one patient with diarrhea and lethargy; one patient with somnolence, decreased appetite, and weight loss; and one patient each with rash, somnolence, or aggression. With the exception of the adverse event of rash, all adverse events were considered to be related to study medication.

793 **Figure 2.** Cumulative response curve for percent reduction in monthly convulsive seizure

794 frequency during the combined titration and maintenance periods.



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796 The vertical dashed lines represent 25%, 50%, and 75% reduction in convulsive seizure frequency and the
797 percentages represent the proportion of patients in each treatment group who met or exceeded each response level.
798 *P* values and are for comparison with placebo and were estimated by logistic regression as described in the Table 2
799 footnotes.