Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial

Lieven Lagae, Joseph Sullivan*, Kelly Knupp, Linda Laux, Tilman Polster, Marina Nikanorova, Orrin Devinsky, J Helen Cross, Renzo Guerrini, Dinesh Talwar, Ian Miller, Gail Farfel, Bradley S Galer, Arnold Gammaitoni, Arun Mistry, Glenn Morrison, Michael Lock, Anupam Agarwal, Wyman W Lai, Berten Ceulemans, for the FAiRE DS Study Group*

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 In this randomised, double-blind, placebo-controlled clinical trial, we enrolled children and young adults with Dravet syndrome. After a 6-week observation period to establish baseline monthly convulsive seizure frequency (MCSF; convulsive seizures were defined as hemiclonic, tonic, clonic, tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs), patients were randomly assigned through an interactive web response system in a 1:1:1 ratio to placebo, fenfluramine 0·2 mg/kg per day, or fenfluramine 0·7 mg/kg per day, added to existing antiepileptic agents for 14 weeks. The primary outcome was the change in mean monthly frequency of convulsive seizures during the treatment period compared with baseline in the 0·7 mg/kg per day group versus placebo; 0·2 mg/kg per day versus placebo was assessed as a key secondary outcome. Analysis was by modified intention to treat. Safety analyses included all participants who received at least one dose of study medication. This trial is registered with ClinicalTrials.gov with two identical protocols NCT02682927 and NCT02826863.

Findings Between Jan 15, 2016, and Aug 14, 2017, we assessed 173 patients, of whom 119 patients (mean age 9·0 years, 64 [54%] male) were randomly assigned to receive either fenfluramine 0·2 mg/kg per day (39), fenfluramine 0·7 mg/kg per day (40) or placebo (40). During treatment, the median reduction in seizure frequency was 74·9% in the fenfluramine 0·7 mg/kg group (from median 20·7 seizures per 28 days to 4·7 seizures per 28 days), 42·3% in the fenfluramine 0·2 mg/kg group (from median 17·5 seizures per 28 days to 12·6 per 28 days), and 19·2% in the placebo group (from median 27·3 per 28 days to 22·0 per 28 days). The study met its primary efficacy endpoint, with fenfluramine 0·7 mg/kg per day showing a 62·3% greater reduction in mean MCSF compared with placebo (95% CI 47·7–72·8, p<0·0001); fenfluramine 0·2 mg/kg per day showed a 32·4% reduction in mean MCSF compared with placebo (95% CI 6·2–52·3, p=0·0209). The most common adverse events (occurring in at least 10% of patients and more frequently in the fenfluramine groups) were decreased appetite, diarrhoea, fatigue, lethargy, somnolence, and decreased weight. Echocardiographic examinations revealed valve function within the normal physiological range in all patients during the trial and no signs of pulmonary arterial hypertension.

Interpretation In Dravet syndrome, fenfluramine provided significantly greater reduction in convulsive seizure frequency compared with placebo and was generally well tolerated, with no observed valvular heart disease or pulmonary arterial hypertension. Fenfluramine could be an important new treatment option for patients with Dravet syndrome.

Funding Zogenix.

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 are inadequate for most patients, and approximately 45% of patients have more than three tonic-clonic seizures per month despite multiple antiepileptic drugs.[3] These patients also have 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

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*Contributed equally

Department of Paediatric Neurology, University of Leuven, Leuven, Belgium (Prof L Lagae MD); **University of California, San Francisco Benioff Children's Hospital, San Francisco, CA, USA** (J Sullivan MD); **University of Colorado, Children's Hospital Colorado, Aurora, CO, USA** (K Knupp MD); **Northwestern University Feinberg School of Medicine, Chicago, IL, USA** (L Laux MD); **Mara Hospital, Bielefeld, Germany** (T Polster MD); **Danish Epilepsy Centre, Dianalund, Denmark** (M Nikanorova MD); **NYU Langone Medical Center, New York, NY, USA** (Prof O Devinsky MD); **UCL Great Ormond Street NIHR BRC Institute of Child Health, London, UK** (Prof J H Cross MBChB); **University of Florence, Florence, Italy** (Prof R Guerrini MD); **University of Arizona Health Sciences Center, Tucson, AZ, USA** (D Talwar MD); **Nicklaus Children's Hospital, Miami, FL, USA** (I Miller MD); **Zogenix, Emeryville, CA, USA** (G Farfel PhD, B S Galer MD, A Gammaitoni PharmD, A Mistry MBChB, G Morrison PhD, M Lock PhD, A Agarwal MD); **CHOC Children's, Orange, CA, USA** (W W Lai MD); **and Department of Paediatric Neurology, University of Antwerp, Edegem, Belgium** (Prof B Ceulemans MD); **for the FAiRE DS Study Group**

Correspondence to: Dr Arnold Gammaitoni, Zogenix, Emeryville, CA 94608, USA **agammaitoni@zogenix.com**

Research in context

Evidence before this study

We searched PubMed 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 might possess anti-seizure activity. Two cohorts of patients with Dravet syndrome have been given low doses of fenfluramine for up to 30 years with clinically 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 of 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 (0·2–0·7 mg/kg per day to a maximum daily dose of 26 mg) added to existing antiepileptic therapy could be effective in reducing the frequency of convulsive seizures in patients with Dravet syndrome. The safety results indicate that patients given these doses of fenfluramine might have 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 physiological range in all patients and none of the patients developed pulmonary arterial hypertension.

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 given up to 220 mg per day.[9] Compassionate use approval was granted by the Government of Belgium in 2002 to allow patients with Dravet syndrome to be given fenfluramine under a treatment protocol. Some of these patients have been given daily fenfluramine for up to 30 years with sustained, clinically significant reductions in seizure frequency, without evidence of cardiopulmonary disease.[11–13] The mean daily doses reported as of the most recent visit in the two cohorts of Belgian patients were 0·27 mg/kg per day (range 0·13–0·46) and 0·35 mg/kg per day (0·16–0·69).[14] We aimed to investigate the efficacy of fenfluramine hydrochloride oral solution to treat seizures in children and young adults with Dravet syndrome.

See Online for appendix

Methods

Study design

In these two identical phase 3, multinational, randomised, double-blind, placebo-controlled clinical trials we compared two different doses of fenfluramine to placebo in children and young adults with Dravet syndrome. One trial was done in the USA 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 datasets before 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 before enrolling in the trial.

Participants

Eligible patients were aged 2–18 years, with a medical history to support a clinical diagnosis of Dravet syndrome (appendix), and in whom seizures had not been completely controlled by their current regimen of antiepileptic drugs or other therapies. Patients were recruited from investigators' clinical practice populations, referrals, and advertising where permitted. Based on medical records or caregiver reports, patients must have had at least four convulsive seizures in a 4-week period during the 12 weeks before entering the screening (baseline) period of the trial. Genetic testing was done 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 4 weeks before screening and were expected to remain stable throughout trial participation. Key exclusion criteria before starting the screening period included a history of pulmonary hypertension; a history of cardiovascular or cerebrovascular disease, including aortic or mitral valve regurgitation as established 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 before screening; a positive urine test for tetrahydrocannabinol; and a positive whole blood test for cannabidiol at screening. Potential patients were monitored in a 6-week baseline period to establish seizure frequency and determine eligibility. Echocardiographic examinations were done during the baseline period, and patients showing aortic 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 should have had at least six convulsive seizures during the baseline period with at least two in the first 3 weeks and at least two in the last 3 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. The Epilepsy Study Consortium confirmed that each patient met the diagnostic criteria for study entry.

Randomisation and masking

After the 6-week baseline period, eligible patients were randomly assigned 1:1:1 to treatment with placebo, fenfluramine hydrochloride 0·2 mg/kg per day (base equivalent 0·17 mg/kg per day), or fenfluramine hydrochloride 0·8 mg/kg per day (base equivalent 0·69 mg/kg per day), with the maximum daily dose limited to 30 mg per day (base equivalent 25·9 mg). All doses of fenfluramine are expressed in the manuscript as base-equivalent doses.

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 enrolled patients, but during the drafting of the statistical analysis plan and after observing the age distribution of the study population in a study of Dravet syndrome,[15] the stratification regimen was changed in the statistical analysis plan to achieve an age distribution of 25% in patients younger than 6 years. 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 people involved in acquiring and assessing data were masked to treatment group assignment.

Procedures

Parents or caregivers administered fenfluramine 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 h apart. During the first 2 weeks (titration period), we titrated patients in the fenfluramine 0·7 mg/kg per day group to their final dose, starting with 0·2 mg/kg per day for 4 days, 0·4 mg/kg per day for 4 days, and then reaching the final dose. The other groups underwent dummy titrations. After the titration period, patients were maintained on their final dose for an additional 12 weeks (maintenance period). At the conclusion of the 14-week treatment period (titration plus maintenance), eligible patients choosing to continue in an optional open-label extension study (NCT02823145) underwent a blinded 2-week transition period, and patients exiting the study underwent a 2-week taper of medication and a safety follow-up, 3–6 months after the last dose of active study medication, depending on the duration of exposure.

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 or 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 done at each in-clinic study visit (during baseline, at group assignment, 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 (preschool for children aged 2–5 years)[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 done during the screening period, after 6 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 organisation, Biomedical Systems (St. Louis, MO), which served as the echocardiography and electrocardiogram core laboratory for this study. In addition, we established an International Paediatric Cardiology Advisory Board of experienced academic cardiologists with expertise in echocardiography to provide guidance and recommendations regarding cardiac assessments throughout the phase 3 programme. Cardiac valve regurgitation severity was graded as absent, trace, mild, moderate, or severe. Valvular heart disease was defined as the presence of mitral valve regurgitation of at least moderate severity or aortic valve regurgitation of mild or higher severity.[17] We considered pulmonary hypertension to be present when pulmonary arterial systolic pressure exceeded 35 mm Hg.[18]

Outcomes

Monthly convulsive seizure frequency (MCSF; convulsive seizures were defined as hemiclonic, tonic, clonic,

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tonic-atonic, generalised tonic-clonic, and focal with clearly observable motor signs) was expressed per 28 days. The primary endpoint was the comparison of change in mean MCSF between the baseline period and the combined titration and maintenance periods in patients given fenfluramine 0·7 mg/kg per day compared with placebo. Key secondary endpoints were comparison of change in mean MCSF between the baseline period and the combined titration and maintenance period in patients given fenfluramine 0·2 mg/kg per day compared with placebo, comparison of both fenfluramine groups independently with placebo on the proportion of patients who achieved at least 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.

All primary, key secondary, and other secondary outcomes were prespecified (with the exception of those labelled as post hoc).

Other secondary outcomes included a responder analysis (ie, 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 had 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 or 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 Quality of Life in Childhood Epilepsy Scale[19] and Pediatric Quality of Life Inventory[20] were usd to assess patient quality of life. The Quality of Life in Childhood Epilepsy Scale is a low-burden parent or caregiver-completed assessment that looks at how epilepsy affects day-to-day functioning of their child in various life areas, including physical activities, wellbeing, cognition, social activities, behaviour, and general health. Its subscales and total score are expressed on a scale of 0–100, with higher values representing better quality of life. The Pediatric Quality of Life Inventory 4.0 is a quality-of-life scale that assesses 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 0–100, in which higher scores represent better quality of life.

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 SD 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 patients with Dravet syndrome. 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%, using a two-sided *t* test at 0·05 significance.

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 95% CI endpoints were exponentiated to yield an estimate of the placebo-adjusted response. The comparison of fenfluramine 0·2 mg/kg per day with placebo for change in convulsive seizure frequency from baseline to the combined titration and maintenance periods was obtained from the same analysis. The proportion of patients who achieved at least a 50% reduction in convulsive seizure frequency was compared using a logistic regression model that incorporated the same factors as the primary endpoint analysis. The Wilcoxon rank sum test was used to compare the longest seizure-free interval between groups; 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 0·05 across the analyses of the primary and five key secondary endpoints. No correction for multiplicity was done for additional secondary endpoints. The primary and all key secondary endpoint analyses were done on the modified intention-to-treat population, defined as all patients who received at least one dose of study medication and had at least 1 week of post-treatment seizure diary data. These analyses were also done 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 had a treatment compliance rate of at least 80%. Safety analyses included all participants who received at least one dose of study medication. Missing data were not imputed.

The secondary responder analysis was assessed using logistic regression as described. 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 with 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, who designed the study with input from the investigators. Zogenix and the contracted clinical research organisation (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 had access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From Jan 15, 2016, to Aug 14, 2017, we screened 173 patients for eligibility, of whom 54 patients were ineligible. The two most common reasons for exclusion were the presence of predefined exclusionary cardiovascular or cardiopulmonary findings, primarily trace mitral or trace aortic valve regurgitation during screening echocardiographic examination (23) and failure to meet other entry requirements (19). 119 patients were enrolled and randomly assigned to a treatment group (figure 1). 40 patients were assigned to receive placebo, 39 patients were assigned to receive fenfluramine 0·2 mg/kg per day, and 40 patients were assigned to receive fenfluramine 0·7 mg/kg per day. Nine patients withdrew before completion of the trial, three in the placebo group (one lack of efficacy, two patient or guardian decision) and six in the fenfluramine 0·7 mg/kg per day group (five for adverse events, one patient or guardian decision). All patients reached the target dose, but six patients did not tolerate the 0·7 mg/kg per day dose as add-on therapy and either reduced the dose (three patients) or discontinued the trial (three patients). Upon completion of the 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 mean age of patients was 9·0 years (SD 4·7), and the baseline median convulsive seizure frequency per month ranged from 17·5–27·3 among the three treatment groups. Patients were being treated at baseline with a mean of 2·4 antiepileptic drugs (SD 1, median 2; range 0–5), which most commonly included valproate (n=71, 60%), clobazam (70, 59%), topiramate (30, 25%), and levetiracetam (26, 22%). 58 (49%) patients had previously been treated with stiripentol and 31 (26%) with cannabidiol. Overall mean compliance to study medication was more than 90% in each treatment group, as reported by caretakers in the daily diary and verified against returned medication. 12 patients, all in the fenfluramine

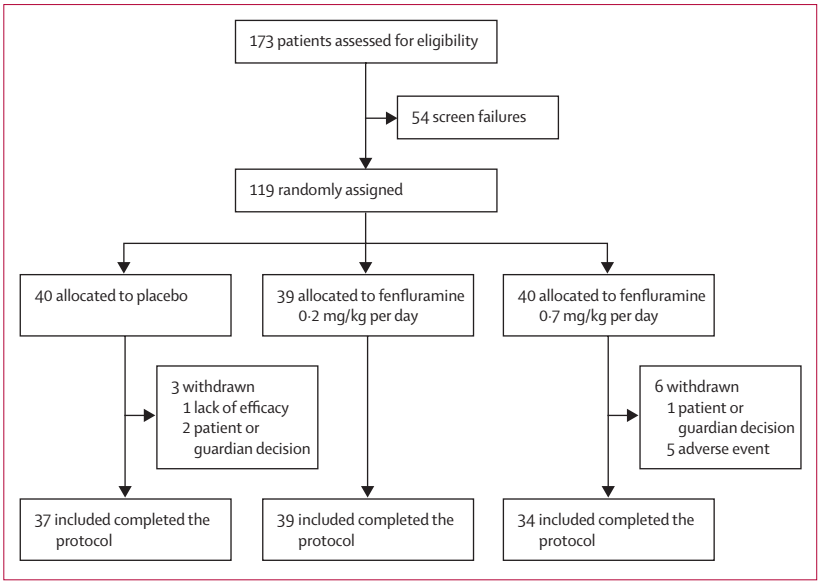

Figure 1: **Trial profile**

	Fenfluramine 0·7 mg/kg per day (n=40)	Fenfluramine 0·2 mg/kg per day (n=39)	Placebo (n=40)	Total (n=119)
Age, years				
Mean (SD)	8·8 (4·4)	9·0 (4·5)	9·2 (5·1)	9·0 (4·7)
Range	2–18	2–17	2–18	2–18
Patients younger than 6 years	11 (28)	9 (23)	11 (28)	31 (26)
Male	21 (52)	22 (56)	21 (52)	64 (54)
Race				
White	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)
Bodyweight (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	33 (82)	31 (80)	31 (78)	95 (80)
Region				
USA 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)
Concomitant antiepileptic drugs				
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 given maximum dose of fenfluramine (26 mg per day)	12 (30)	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 (range)	20·7 (4·8–124)	17·5 (4·7–623·5)	27·3 (3·3–147·3)	24·1 (3·3–623·5)

Data are number of participants (%) unless otherwise specified. BMI=Body-mass index. *Privacy laws in some regions preclude disclosure of particular personal information.

Table 1: **Demographics and baseline convulsive seizure frequency**

0·7 mg/kg per day group, were given the maximum daily dose of 26 mg fenfluramine during the combined titration and maintenance periods.

Seizure frequency during the 14-week treatment period declined by a median 74·9% (from median 20·7 seizures to 4·7 seizures per 28 days) in the fenfluramine 0·7 mg/kg per day group, 42·3% (17·5 seizures to 12·6 seizures per 28 days) in the fenfluramine 0·2 mg/kg per day group, and 19·2% (27·3 seizures to 22·0 seizures per 28 days) in the placebo group (table 2). The study met its primary efficacy endpoint with high statistical significance. Patients in the fenfluramine 0·7 mg/kg per day group had a 62·3% greater reduction in mean MCSF over the 14-week treatment period compared with placebo (p<0·0001). The fenfluramine 0·2 mg/kg per day group had a significant 32·4% reduction in mean MCSF compared with placebo (p=0·0209). A significantly greater proportion of patients given either dose of fenfluramine had a reduction in MCSF in all categories (≥25%, ≥50%, or ≥75%) during the treatment period compared with patients in the placebo group (figure 2, table 2).

During the treatment period, 27 (68%) of 40 patients in the fenfluramine 0·7 mg/kg per day group and 15 (38%) of 39 patients in the fenfluramine 0·2 mg/kg per day group had a reduction in convulsive seizure frequency of

	Fenfluramine 0·7 mg/kg per day (n=40)	Fenfluramine 0·2 mg/kg per day (n=39)	Placebo (n=40)
Primary and key secondary endpoints*			
Change in convulsive seizure frequency per 28 days			
Estimated difference from placebo, % (95% CI)†	−62·3 (−47·7 to −72·8)‡	−32·4 (−6·2 to −51·3)§	..
p value	p<0·0001	p=0·0209	..
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)	15·0 (4·5 to 50·0)	4·8 (1·5 to 15·0)	..
Longest seizure-free interval, days			
Mean (SD)	32·9 (27·5)	26·0 (31·7)	10·6 (6·0)
Median (range)	25·0 (2 to 97)§	15 (3 to 106)§	9·5 (2 to 23)
Estimate of median treatment difference (95% CI)	15·5 (6 to 25)	4·5 (0 to 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)	22·3 (6 to 84)	4·1 (2 to 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)	55·1 (6 to 526)	12·0 (1·4 to 102)	..
100% reduction in convulsive seizure frequency			
n (%)‖	3 (8)	3 (8)	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 (range)	0 (0 to 8)	0·3 (0 to 16)	1·7 (0 to 24)
p value	p<0·0001	p=0·0822	..
Convulsive seizure frequency per 28 days			
Percentage change from baseline, median (range)	−74·9 (−100 to 196·4)	−42·3 (−100 to 197·6)	−19·2 (−76·1 to 51·8)
p value	p<0·0001	p=0·2035	..
Total seizure frequency per 28 days			
Percentage change from baseline, median (range)	−68·3 (−100 to 35·6)	−41·1 (−100 to 292)	−16·2 (−77·6 to 601)
p value	p<0·0001	p=0·0202	..
Other** seizure frequency per 28 days			
Patients having other seizure types (n)	24	23	21
Percentage change from baseline, median (range)	−76·0 (−100 to 69·2)	−50·6 (−100 to 534)	−55·6 (−100 to 723·6)
p value	p=0·0458	p=0·7585	..

(Table 2 continues on next page)

	Fenfluramine 0·7 mg/kg per day (n=40)	Fenfluramine 0·2 mg/kg per day (n=39)	Placebo (n=40)
(Continued from previous page)			
Non-seizure outcomes			
Change in bodyweight (kg) by age group, median (range; n)			
2–4 years	0·4 (–1·5 to 1·1; n=7)	–0·1 (–1·6 to 0·7; n=8)	1·1 (–0·2 to 1·4; n=9)
5–12 years	–0·9 (–5·9 to 0·8; n=23)	0·3 (–9·0 to 3·7; n=21)	1·0 (–1·1 to 3·6; n=19)
13–18 years	–2·6 (–4·5 to 1·6; n=8)	–0·4 (–9·8 to 3·4; n=10)	0·2 (–0·6 to 7·6; n=11)
Clinical Global Impression of Improvement			
Parent or caregiver rating			
Very much improved or much improved, n (%)	22 (55)	16 (41)	4 (10)
p value	p<0·0001	p=0·0036	..
Investigator rating			
Very much improved or much improved, n (%)	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	..
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	..
Behavioral Rating Inventory of Executive Function‡‡§§			
Behavioral Regulatory 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 to –0·52	–3·4 (8·6) –6·82 to 0·01	3·0 (8·7) –0·54 to 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 to 1·12	–1·0 (16·4) –7·51 to 5·44	5·9 (19·1) –2·02 to 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) 95% CI	–11·0 (29·1) –21·91 to –0·15	–4·4 (22·3) –13·27 to 4·38	8·9 (24·9) –1·35 to 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 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 used for other secondary outcomes. ||Because of the small number of patients with 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. 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 per 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 per day to placebo at the 75% responder level, the OR was 39·0 and relative risk was 20.

Table 2: **Efficacy endpoints**

at least 50%, compared with five (12%) of 40 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 per day group (p<0·0001), 15 days in the fenfluramine 0·2 mg/kg per 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 seen in three (8%) patients in the fenfluramine 0·7 mg/kg per day group, three (8%) patients in the fenfluramine 0·2 mg/kg per day group, and 0 patients in the placebo

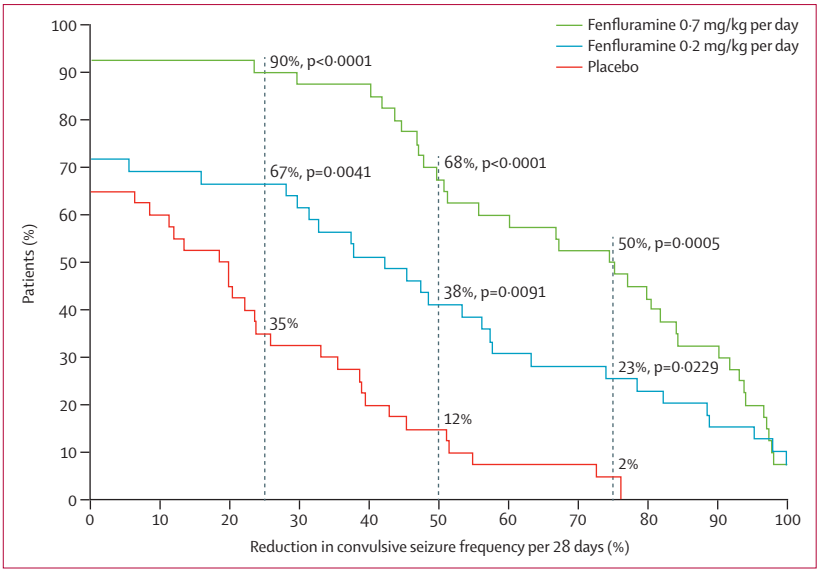

Figure 2: **Cumulative response curve for percentage reduction in monthly convulsive seizure frequency during the combined titration and maintenance periods**

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

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

Data are n (%).

Table 3: **Non-cardiovascular adverse events occurring in at least 10% of patients in any treatment group**

group (table 2), and only one seizure was reported in the entire 14-week treatment period by seven (18%) patients in the 0·7 mg/kg per day group, two (5%) patients in the 0·2 mg/kg per day group, and 0 patients in the placebo group. In addition to its antiseizure activity, patients in the 0·7 mg/kg per 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 modified intention-to-treat population.

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

At the end of the treatment period, 22 (55%) patients in the fenfluramine 0·7 mg/kg per day group (p<0·0001) and 16 (41%) in the fenfluramine 0·2 mg/kg per day group (p=0·0036) were rated as much improved or very much improved by their caretaker, compared with four (10%) in the placebo group (table 2). When assessed by the investigator, 25 (62%) patients in the fenfluramine 0·7 mg/kg per day group (p<0·0001), 16 (41%) in the fenfluramine 0·2 mg/kg per day group (p=0·0032), and four (10%) in the placebo group were rated much improved or very much improved (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, total scores on the parent-reported Pediatric Quality of Life Inventory at the end of treatment improved by a mean of 5·9 points in the fenfluramine 0·7 mg/kg per day group (SD 15·1, p=0·0198) and 6·8 points in the fenfluramine 0·2 mg/kg per day group (SD 11·2, p=0·0029), compared with a small decrease or worsening in the placebo group (–1·6, SD 10·4).

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

Adverse events were reported in 26 (65%) of 40 patients in the placebo group, 37 (95%) of 39 patients in the 0·2 mg/kg per day group, and 38 (95%) of 40 patients in the fenfluramine 0·7 mg/kg per day group. A summary of non-cardiovascular adverse events that occurred in at least 10% of patients in any treatment group is presented in table 3. The most common non-cardiovascular adverse events in fenfluramine-treated patients were decreased appetite, diarrhoea, nasopharyngitis, lethargy, somnolence, and pyrexia. In patients with non-cardiovascular adverse events, 94 (93%) of 101 patients were mild to moderate in severity, including 35 (92%) of 38 patients in the fenfluramine 0·7 mg/kg per day group, 35 (95%) of 37 patients in the fenfluramine 0·2 mg/kg per day group, and 24 (92%) of 26 patients in the placebo group.

Because fenfluramine had been marketed at higher doses as an anorectic drug, bodyweight was monitored throughout the trial. Median changes in bodyweight by age group and treatment are presented in table 2. A change from baseline of at least 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 per day group, five (13%) patients had weight loss, ranging from 8·4–21·9% of bodyweight; the patient who lost 21·9% of bodyweight was being actively managed for obesity by a nutritionist to lose excess bodyweight before and during the trial. In the fenfluramine 0·7 mg/kg per day group, eight (20%) patients lost weight, ranging from 7·2–11·4% of bodyweight. One patient in the fenfluramine 0·7 mg/kg per 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 per day group, and five (13%) patients in the fenfluramine 0·7 mg/kg per day group. The most common serious adverse events included hospital admission for status epilepticus in two (5%) patients in the placebo group, one (3%) patient in the fenfluramine 0·2 mg/kg per day group, and two (5%) patients in the fenfluramine 0·7 mg/kg per day group.

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%) patients in the placebo group, seven (18%) patients in the fenfluramine 0·2 mg/kg per day group, and nine (23%) patients in the fenfluramine 0·7 mg/kg per day group had at least one echocardiographic finding with trace mitral or aortic regurgitation, which is a physiological and normal finding seen in healthy children and young adults.[24]

After 14 weeks of treatment, patients in the fenfluramine 0·7 mg/kg per day group had 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 (SUDEP).[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 in an attempt to control seizures, 45% of patients continued to have at least four tonic-clonic seizures per 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 health questionnaire that are equivalent to someone in the general population living with a major illness (ie, heart disease, diabetes, cancer).[25] These reports illustrate the high unmet need for new and better therapies in Dravet syndrome.

In this randomised, double-blind clinical trial, fenfluramine oral solution resulted in a significant reduction in the frequency of convulsive seizures compared with placebo in children and young adults with Dravet syndrome. In addition, significantly higher responder rates were observed compared with placebo, particularly in patients who had at least a 50% or 75% reduction in the frequency of convulsive seizures. Patients included in our trial had a high seizure burden as previously described, with an average of about 1·5 convulsive seizures per day (mean baseline convulsive seizure frequency per 28 days 40·3, SD 64·0). On this background of high seizure burden, 25% of patients in the 0·7 mg/kg per day and 13% of patients in the 0·2 mg/kg per day group had either one or no convulsive seizures for the entire 14-week study, further illustrating the efficacy of fenfluramine. Both the investigators and the parents or 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 whether 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. Both seizure burden and neuronal sodium channel dysfunction caused by *SCN1A* mutations might contribute to cognitive dysfunction in patients with Dravet syndrome,[28,29] and reports suggest 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 our 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 affect 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 reported more often in patients given fenfluramine than with placebo. Fenfluramine was previously marketed as an appetite suppressant and 21–38% of patients in the active treatment groups had decreases in appetite; weight loss above the 7% threshold was observed in 13% of patients in the fenfluramine 0·2 mg/kg per day group, and in 20% of patients in the fenfluramine 0·7 mg/kg per day group. Serious adverse events occurred with similar frequency across all three treatment groups.

Cardiovascular safety is an important outcome measure when evaluating the use of fenfluramine to treat patients with Dravet syndrome.[9] Based on reports of cardiac valve disease in adult obese patients given up to 220 mg per 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[17] examined the records of the patients in the original FDA report and found that the risk of severe valvulopathy was increased 9·2 times (95% CI 2·1–40·8) in patients given at least 60 mg per day compared with patients given less than 40 mg per day.[31] Others have identified 3 months' use of fenfluramine as a threshold for increased risk of valvulopathy[32] and 6 months' use of fenfluramine as a threshold for increased risk of pulmonary arterial hypertension.[32–35] In the present trial, all patients were given 26 mg per day or less 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 2-week transition period at the end of the maintenance period, all echocardiographic examinations revealed valve function within the normal physiological range, and no pulmonary arterial hypertension was observed in any patient at any time. 21 patients, including five patients in the placebo group, had at least one echocardiographic finding with trace mitral 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 physiological finding seen in healthy children and adults.[24,36,37] Although our observations suggest a dose response for the finding of trace regurgitation, this association disappeared with continued treatment in the long-term extension of this study. None of these patients, or any other patient with Dravet syndrome enrolled in the open-label extension study of fenfluramine, had 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 timepoint, 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 (13%) of 173 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 children aged 10–12 years. Webb and colleagues[39] reported a cross-sectional prevalence of trace or physiological mitral regurgitation of 59 (15%) of 396 in children aged 10–12 years.

Our conclusions about the cardiovascular safety of fenfluramine are limited by the 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 per 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 fenfluramine treatment with ongoing echocardiographic examinations.

Although we used 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 in fenfluramine-treated patients was decreased appetite, which occurred in 38% of patients in the 0·7 mg/kg per day dose group.

This randomised controlled clinical trial showed 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 showing 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 assess long-term efficacy and safety of fenfluramine for the treatment of Dravet syndrome, including its effect on cardiac valves.

Contributors

LLag, JS, BC, AG, BSG, GF, and ML designed the study. LLag, JS, KK, LLau, TP, MN, OD, JHC, RG, DT, IM, and BC collected data. ML analysed the data. All authors contributed equally to the interpretation of the efficacy and non-cardiovascular safety findings. WWL and AA provided the primary interpretation of the cardiovascular safety findings. 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, LLag, BC, and JS and was reviewed by all authors. GF, BSG, AG, LLag, JS, ML, and BC were the primary writers of the manuscript. All authors contributed equally to the review and revision of the manuscript, and all authors approved the final version.

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

Declaration of interests
LLag received grants, personal fees, and other as a consultant or speaker from Zogenix during the conduct of the study; other as a consultant or speaker from LivaNova, grants and other as a consultant or speaker from UCB, other as a speaker from Shire, and other as a speaker from Eisai outside the submitted work. LLag 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 served 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. LLau 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 adviser from GW Pharma, other as a speaker or adviser from Shire, other as an adviser or speaker from Zogenix, other as speaker from Biomarin, and other as adviser 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 or 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, and 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 might 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.

Data sharing
Zogenix does not have a data sharing policy.

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