Received: 15 May 2020 | Revised: 16 July 2020 | Accepted: 16 July 2020

DOI: 10.1111/epi.16638

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Cardiovascular safety of fenfluramine in the treatment of Dravet syndrome: Analysis of an ongoing long-term open-label safety extension study

Wyman W. Lai[1] | **Bradley S. Galer**[2] | **Pierre C. Wong**[3] | **Gail Farfel**[2] | **Milka Pringsheim**[4,5] | **Martin G. Keane**[6] | **Anupam Agarwal**[2]

[1]Children's Hospital of Orange County, Orange, CA, USA

[2]Zogenix, Inc., Emeryville, CA, USA

[3]Children's Hospital Los Angeles, Los Angeles, CA, USA

[4]Department of Pediatric Cardiology, German Heart Centre Munich, Munich, Germany

[5]Pediatric Neurology, Schön Klinik Vogtareuth, Vogtareuth, Germany

[6]Temple University Hospital, Philadelphia, PA, USA

Correspondence
Bradley S. Galer, Executive Vice President and Chief Medical Officer; Zogenix, Inc., 5858 Horton Street, Suite 455, Emeryville, CA 94608, USA.
Email: bgaler@zogenix.com

Funding Information
This study was funded by Zogenix, Inc. (Emeryville, CA, USA). Several of the funder's employees are authors of this paper and, accordingly, participated in the design and conduct of this study; collection, management, analysis, and interpretation of data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Abstract

Objective: Fenfluramine, which was previously approved as a weight loss drug, was withdrawn in 1997 when reports of cardiac valvulopathy emerged. The present study was conducted in part to characterize the cardiovascular safety profile of low-dose fenfluramine when used in a pediatric population to reduce seizure frequency in patients with Dravet syndrome.

Methods: Patients 2- to 18-years-old with Dravet syndrome who had completed any of three randomized, placebo-controlled clinical trials of fenfluramine were offered enrollment in this open-label extension (OLE) study. All patients were treated with fenfluramine starting at a dose of 0.2 mg/kg/day (oral solution dosed twice per day), which was titrated to maximal effect with a dose limit of 0.7 mg/kg/day (maximum 26 mg/day) or 0.4 mg/kg/day (maximum 17 mg/day) in patients receiving concomitant stiripentol. Standardized echocardiographic examinations were conducted at Week 4 or 6 and then every 3 months during the OLE study to monitor cardiac valve function and structure and pulmonary artery pressure. The primary end point for the echocardiography analysis was the number of patients who developed valvular heart disease or pulmonary artery hypertension (PAH) during treatment.

Results: A total of 232 patients were enrolled in the study. The average age of patients was 9.1 ± 4.7 years, and 55.2% were male. The median duration of treatment with fenfluramine was 256 days (range = 58-634 days), and the mean dose of fenfluramine was 0.41 mg/kg/day. No cases of valvular heart disease or PAH were observed.

Significance: Longitudinal echocardiography over a median 8.4 months of treatment with fenfluramine suggests a low risk of developing cardiac valvulopathy and PAH when used to treat pediatric patients with Dravet syndrome.

Meeting Presentation: Parts of this analysis were presented as a poster at the 72nd Annual Meeting of the American Epilepsy Society; December 3, 2018; New Orleans, LA, USA.

KEYWORDS
Dravet syndrome, epilepsy, fenfluramine

1 | INTRODUCTION

Dravet syndrome is a severe, treatment-resistant epileptic encephalopathy that has its onset in the first year of life and is characterized by a high seizure burden and significant comorbid behavioral, motor, and neurodevelopmental abnormalities.[1-3] Dravet syndrome confers an elevated risk of early mortality compared to other forms of epilepsy,[4,5] and is associated with a substantial health-related economic impact.[6] Current standard of care includes polypharmacy, often including three or more concomitant antiepileptic drugs (AEDs), usually providing inadequate seizure control in most patients.[7] Thus there remains a significant unmet medical need for an effective therapy for this debilitating condition.

The anticonvulsant activity of fenfluramine was first recognized in the 1980s, when it was tested in individuals and in small series of patients with treatment-resistant epilepsies.[8] At that time, fenfluramine was marketed globally as a weight loss drug for obese adults, but it was globally withdrawn in 1997 following reports of cardiac valvulopathy in adult patients treated with 60 to 120 mg/day[9,10] with reported onset after ≥3 to 6 months of treatment.[11-16] In addition, pulmonary arterial hypertension (PAH) was reported in some adult patients treated with fenfluramine for weight loss.[17] Following its market withdrawal, the use of fenfluramine to treat patients with Dravet syndrome continued in Belgium, where two small cohorts (n = 10 and n = 9) of patients have now been successfully treated for up to 30 years without development of cardiac disease.[18-20]

In two randomized, placebo-controlled clinical trials, fenfluramine demonstrated a 54.0% and 62.3% greater reduction in mean convulsive seizure frequency compared with placebo.[21,22] In addition, 35% and 50% of patients experienced a ≥75% reduction in major convulsive seizure frequency—a response typically not seen in this refractory epilepsy syndrome.[21,22] As part of these protocols, all patients in these studies underwent echocardiographic examinations before and during treatment, and no cases of cardiac valvulopathy (defined by measures of regurgitation and visualization of valve thickness) or PAH were observed during 15 weeks of treatment with fenfluramine. However, the observation period in these double-blind studies was too short to permit firm conclusions with regard to potential effects of fenfluramine on cardiac valve function in this patient population treated with the doses studied. Here we convey cardiovascular observations from an interim analysis of the ongoing long-term, open-label extension (OLE) study of fenfluramine for treatment of Dravet syndrome, reporting on observations in 232 patients after treatment of up to 1.7 years.

Key Points

- Dravet syndrome patients were treated with fenfluramine (dose 0.2-0.7 mg/kg/day) for a median 256 days (range = 57-634 days)
- Standardized echocardiograms were conducted after 4-6 weeks of treatment and every 3 months thereafter
- No valvular heart disease or pulmonary arterial hypertension was observed in any patient during the interim analysis period
- Low-dose fenfluramine appears to have a low cardiovascular risk profile when used to treat patients with Dravet syndrome

2 | MATERIALS AND METHODS

The protocol for the extension study was reviewed and approved by the institutional review board or ethics committee at each study site before initiation of any study activities. All patients or their legal guardians provided signed consent to participate in the study.

Patients aged 2 to 18 years of age with Dravet syndrome who had successfully completed any of the three double-blind phase 3 clinical trials (Studies 1 and 2: NCT02826863 and NCT02682927; Study 1504: NCT02926898) and were eligible could enroll in the OLE study (NCT02823145). Key inclusion criteria included demonstration during the double-blind study of compliance with electronic diary completion (≥90%), study visit schedule, and study drug accountability. Key exclusion criteria included hypersensitivity to fenfluramine or any excipients in the study medication; current or past history of cardiovascular or cerebrovascular disease, myocardial infarction, or stroke; and current valvular heart disease or PAH that the investigator, the caregiver, the international pediatric cardiology review board, or the independent data and safety monitoring committee deemed to be clinically significant and to warrant discontinuation of study medication. Of note, in the double-blind clinical trials, patients with any grade of mitral or aortic valve regurgitation upon echocardiographic examination during the screening period, including "trace" (defined as regurgitation that is barely detectable[23]), were excluded from

participation. However, patients who had a finding of trace mitral or trace aortic regurgitation during the double-blind phase 3 trials were allowed to continue into the OLE study.

Fenfluramine (ZX008; Zogenix, Inc.) was administered with food as an oral solution of fenfluramine HCl, containing 2.2 mg/mL fenfluramine, at equal doses in the morning and in the evening, approximately 12 hours apart. All patients in the OLE study started treatment with a dose of 0.2 mg/kg/day added to their current AED regimen for the first 4 weeks, regardless of the dose they had received in the double-blind trial. After 4 weeks, the dose could be titrated based on effectiveness and tolerability. As per protocol, dose changes were made in 0.2 mg/kg/day increments with a minimum of 2 weeks between steps. Maximum doses allowed were 0.7 mg/kg/day (up to a limit of 26 mg/day), except in patients who were concomitantly treated with stiripentol, who could receive a maximum of 0.4 mg/kg/day (up to a limit of 17 mg/day). Stiripentol inhibits cytochrome P450 (CYP) enzymes and was shown to increase exposure to fenfluramine in a phase 1 drug-drug interaction study in healthy adults.[24] The selection of the maximum dose of fenfluramine to be used in patients concomitantly treated with a stiripentol-containing AED regimen was estimated to approximate exposure to the 0.7-mg/kg/day dose in patients not using a stiripentol-containing AED regimen. This was accomplished by using a physiology-based pharmacokinetic model based on pharmacokinetic data from the phase 1 study, as well as single-dose pharmacokinetic data from 18 pediatric patients with Dravet syndrome.[25] It is important to note that the addition of fenfluramine did not influence the pharmacokinetics of stiripentol, clobazam, or valproate.

All patients had been on blinded treatment during the double-blind clinical trial and received two echocardiographic examinations during that period. Upon entry into the OLE study, a comprehensive transthoracic echocardiogram using two-dimensional imaging, as well as color flow and spectral Doppler evaluation, was performed. Echocardiograms were repeated at Study Week 4 or 6, and every 3 months thereafter, to assess cardiac valve function and pulmonary artery pressure. Standardized views and machine settings were used throughout the study (Appendix S1). All echocardiograms were read at the ECHO Core Lab (Biomedical Systems/ERT) by two blinded, independent, board-certified cardiologists with arbitration provided by a third blinded, board-certified cardiologist in the event of differing interpretations. Regurgitation of all four cardiac valves was graded as absent, trace, mild, moderate, or severe based on standard criteria.[23,26,27] Readers also evaluated the valves for any morphological or movement abnormalities. PAH was defined as pulmonary artery systolic pressure >35 mm Hg[28] that was confirmed by repeat examination.

Although no clinical practice guidelines exist for direct reference, a diagnosis of "clinically significant valvular heart disease" in the current study was based on the presence of ≥mild aortic or ≥moderate mitral regurgitation seen on transthoracic echocardiography, in addition to findings suggestive of significant valve disease based on both a clinical evaluation and a comprehensive assessment of correlative as well as serial cardiac imaging findings. This definition is consistent with the 1997 US Food and Drug Administration (FDA) case definition of cardiac valvulopathy[9] that was applied retrospectively to define cases when the safety of fenfluramine was under review in 1996-1997.

In particular, if either ≥mild aortic regurgitation or ≥moderate mitral regurgitation was seen on transthoracic echocardiography, these findings needed to be further evaluated in a clinical context to assess for physical signs or symptoms attributable to valve disease. Findings also needed to be further evaluated in the context of reviewing all prior cardiac imaging data to assess for a consistently seen degree of regurgitation, a structural lesion of the aortic or mitral valve, abnormal left ventricular (LV) systolic function with depressed LV ejection fraction, LV dilatation, or left atrial enlargement or reduced valve motion.

Single, 12-lead electrocardiography (ECG) was undertaken during the double-blind studies at baseline, at 6 weeks, and at the end of the study, and in the OLE study at Months 1, 2, and 3, and every 3 months thereafter. The primary end point of the ECG analysis was change from baseline in the QT interval corrected using Fridericia's formula (QTcF).

Patients who enrolled in the OLE study and who received at least one dose of fenfluramine in the OLE study by the analysis cut-off date of March 13, 2018, were included in the cardiovascular safety population. The primary end point was the number of patients who met the definition of clinically significant valvular heart disease (VHD) at any time during the study (ie, cumulative prevalence), whether or not the situation abated. The following secondary end points were assessed: number and percentage of patients with trace or greater regurgitation in the mitral and/or aortic valves at each study visit (ie, point prevalence); change from baseline in regurgitation grade for mitral and aortic valves; assessment of mitral valve regurgitation in patients treated with ≥the mean dose of fenfluramine compared to patients treated with <the mean dose of fenfluramine; number and percentage of patients with PAH; number and percentage of patients demonstrating an increase in pulmonary artery systolic pressure from baseline ≥5, ≥10, and ≥15 mm Hg; and mean maximum change from baseline in pulmonary artery systolic pressure. In addition, the number and percentage of patients demonstrating an increase in QTcF from baseline (≥10, ≥30, and ≥60 ms) or any post-baseline value above the upper limit of normal (450 ms for male and female patients younger than 12 years, 450 ms for male patients 12-18 years, and 470 ms for female patients 12-18 years) were evaluated. Mean daily dose for individual patients was calculated as

the sum of daily doses divided by days of exposure. Data are presented with descriptive statistics. Although this long-term open-label study was conducted to assess safety, no a priori hypothesis testing was planned, as enrollment was based on participation in a prior double-blind, controlled study powered to evaluate efficacy. A post hoc analysis of the point prevalence of trace mitral regurgitation was conducted with the assumption that trace mitral valve regurgitation for individuals could have been persistent over time, leading to data for which results at different time points were correlated with each other. Therefore, the trend of mitral valve regurgitation from baseline of the OLE study through 15 months post-baseline was evaluated using logistic regression for correlated binary data, fitted with generalized estimating equations.[29] This model was constructed using SAS version 9.4 (SAS Institute).

3 | RESULTS

The OLE study population included 232 patients who had enrolled in the OLE study as of the interim cut-off date of March 13, 2018, and who had received at least one dose of fenfluramine. Patient demographics are presented in Table 1. A total of 22 patients (9%) had discontinued the OLE study at the time of the interim analysis. The primary reasons for discontinuation included lack of efficacy (n = 16 [7%]); adverse event (n = 1 [0.4%]); withdrawal by patient or caregiver (n = 3 [1%]); death due to sudden unexpected death in epilepsy (SUDEP) (n = 1 [0.4%]); and physician decision (n = 1 [0.4%]).

The median duration of treatment with fenfluramine was 256 days (range = 58-634 days), and the mean daily dose of fenfluramine was 0.41 mg/kg/day. The distribution of mean daily doses over the course of the interim analysis period was >0-0.2 mg/kg/day (29 patients [13%]), >0.2 to <0.3 mg/kg/day (66 patients [28%]), 0.3-0.5 mg/kg/day (76 patients [33%]), and >0.5-0.7 mg/kg/day (61 patients [26%]). As of the cut-off date for this analysis, a total of 19 patients were titrated to the maximum allowed daily dose of fenfluramine (26 mg/day). In these patients, the mean dose was 0.57 mg/kg/day (range = 0.43-0.69 mg/kg/day). Sixty-three patients (27%) were receiving concomitant stiripentol and had their fenfluramine dose limited to a maximum of 0.4 mg/kg/day.

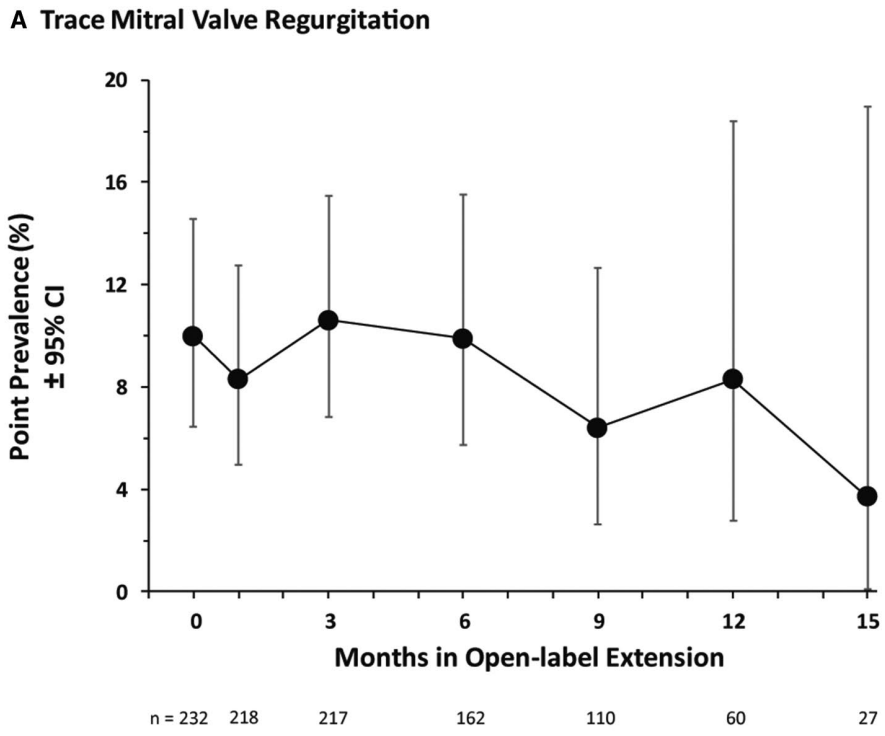
No patient met the FDA case definition of cardiac valvulopathy, and no patient developed VHD or PAH during the interim analysis period of the OLE study. A total of 53 patients (23%) had one or more echocardiograms with trace mitral regurgitation. No patient demonstrated ≥mild mitral valve regurgitation at any time during the OLE study. The point prevalence of trace mitral valve regurgitation was ≤11% at each study visit throughout the entire study period, with no significant change in point prevalence with increasing duration of exposure to fenfluramine ($P = .64$; Figure 1). In most patients, trace mitral regurgitation was a transient finding, often fluctuating between absent and trace regurgitation (Figure 2). In addition, the overall incidence of trace mitral regurgitation was similar in patients treated with ≤the mean daily dose of fenfluramine (0.41 mg/kg/day) in the OLE study population (26/114 [22.8%]) or with >the mean daily dose (27/118 [22.9%]).

A single patient demonstrated trace aortic valve regurgitation at OLE study baseline (1/231 [0.4%]) and again after 30 days of treatment with fenfluramine (1/218 [0.5%]) (see Figure 1). All subsequent echocardiographic observations for this subject through the interim analysis cut-off date showed no (absent) aortic regurgitation.

TABLE 1 Patient demographics

N	232
Age, y	
Mean ± SD	9.1 ± 4.7
Median (minimum, maximum)	9.0 (2, 19)
Age group, n (%)	
<6 y	65 (28.0)
6-18 y	166 (71.6)
>18 y	1 (0.4)
Sex, n (%)	
Male	128 (55.2)
Female	104 (44.8)
Race, n (%)	
White	172 (74.1)
Black or African American	1 (0.4)
Asian	9 (3.9)
American Indian or Alaska Native	2 (0.9)
Other	13 (5.6)
Not reported[a]	35 (15.1)
Ethnicity, n (%)	
Hispanic or Latino	23 (9.9)
Not Hispanic or Latino	159 (68.5)
Not reported[a]	47 (20.3)
Unknown[a]	3 (1.3)
Region, n (%)	
North America	111 (47.8)
Europe/Australia	121 (52.2)
Baseline body mass index (kg/m^2)	
Mean ± SD	17.9 ± 4.2
Median (minimum, maximum)	17.0 (11.8, 39.7)

[a]Privacy laws in some regions/countries precluded disclosure of certain personal information.



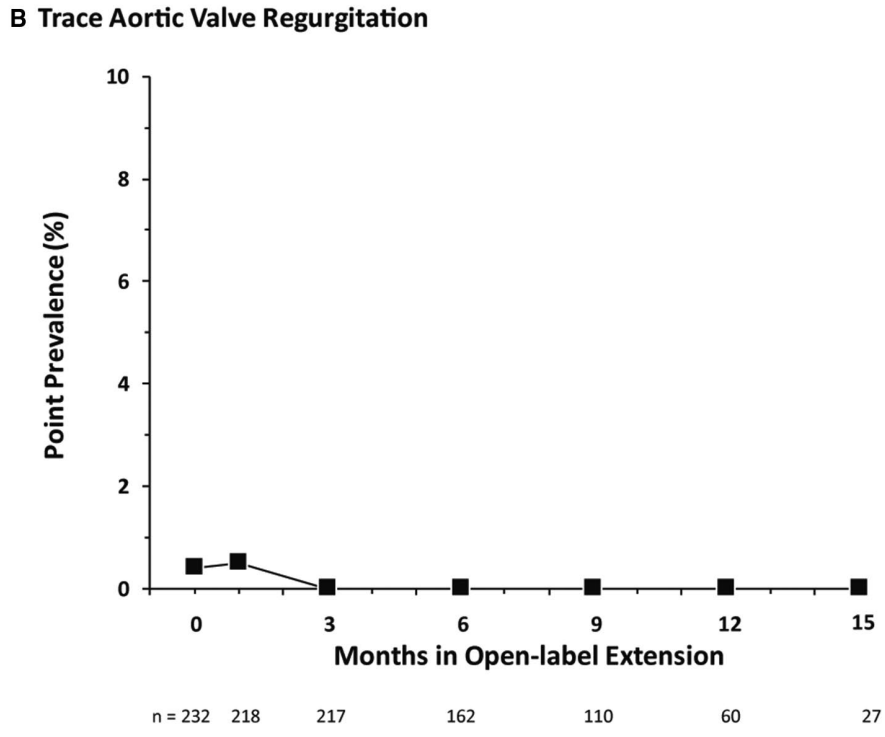


FIGURE 1 Point prevalence of trace regurgitation of the mitral and aortic valves during OLE study treatment with fenfluramine. The decrease in n is due primarily to staggered entry into the OLE study and is not due to patient withdrawal. The *P* value for change in point prevalence of trace mitral valve regurgitation over time was .64 (A). Due to the zero or near zero point prevalence of trace aortic regurgitation, no statistical analysis of change over time was done (B). CI, confidence interval; OLE, open-label extension

All other patients had absent aortic regurgitation for all echocardiograms. The point prevalence of mild tricuspid valve regurgitation ranged from 0% to 3.2% during the OLE study analysis period; all other tricuspid echocardiographic findings were either absent or trace. The point prevalence of mild pulmonic valve regurgitation ranged from 0% to 0.9% during the OLE study period; the remaining 99% of assessments were absent or trace, with the majority being trace. Trace to mild regurgitation of the pulmonary valve or the tricuspid valve is commonly observed in the general population and is considered to be of no physiologic consequence.[23] No morphologic changes or valvular movement abnormalities in any cardiac valve were detected during the study.

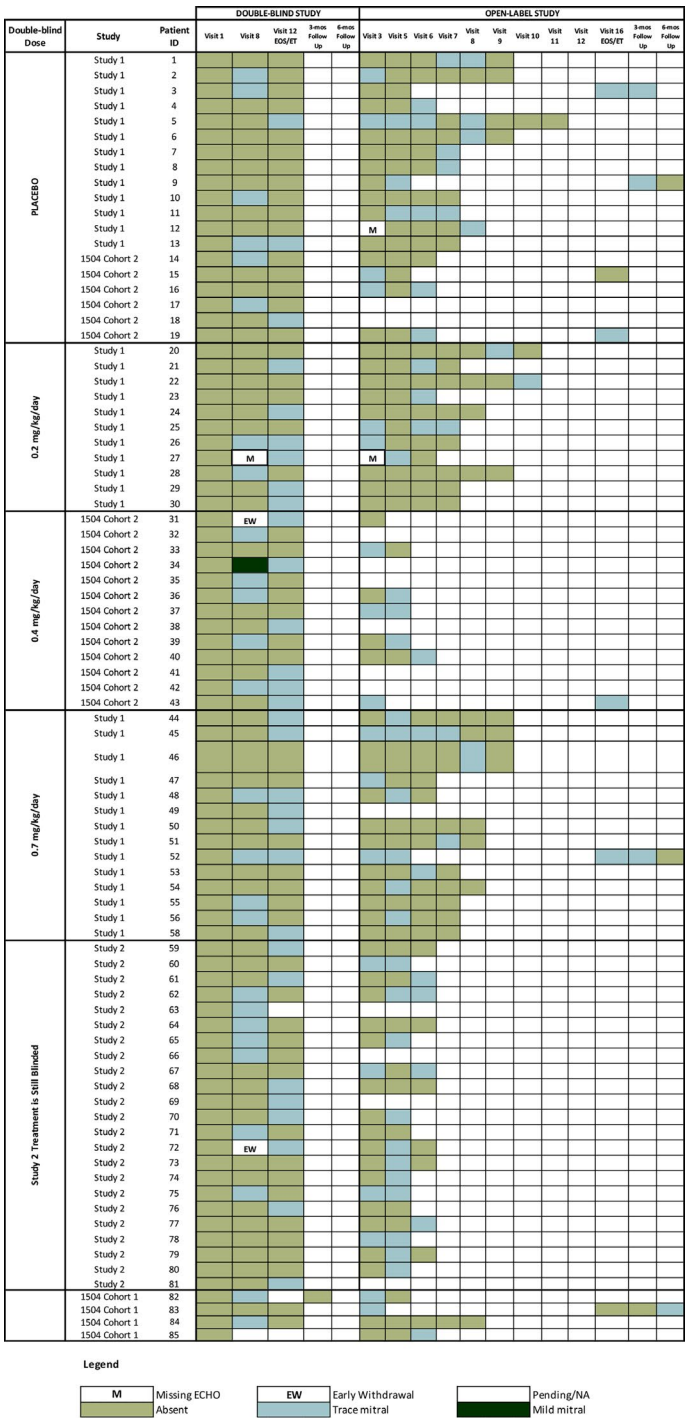


FIGURE 2 Heat map of mitral valve regurgitation for patients enrolled in the open-label extension (OLE) study who demonstrated mitral valve regurgitation of any severity during double-blind clinical trials or during the OLE study. Note: All other patients who are not included in this figure had absent mitral regurgitation at all study visits

No cases of PAH were observed during the OLE study period. Two patients each had a single pulmonary artery systolic pressure reading exceeding 35 mm Hg, and in neither case was the abnormal reading confirmed upon repeated echocardiography. The most recent mean pulmonary artery systolic pressure measurement was 19.16 ± 6.3 mm Hg (mean ± SD) for the 176 patients with evaluable measurements, representing a mean change from baseline of 0.15 ± 7.16 mm Hg (95% CI, −1.2 to 1.5) for the 109 patients with both baseline and most recent visit measurements.

Inspection of ECG intervals and waveforms revealed no effects of fenfluramine on heart rate, atrioventricular conduction, cardiac depolarizations as measured by PR and QRS interval durations, and cardiac repolarization as measured by QT duration. QTcF values were within the normal range for all subjects. No patient had a QTcF exceeding 450 ms, and no patient demonstrated a change from

baseline of QTcF >60 ms. Two patients had a change from baseline of QTcF >30-60 ms.

4 | DISCUSSION

Fenfluramine has resulted in 30% and 50% of patients experiencing ≥75% reduction in convulsive seizure frequency in two double-blind, placebo-controlled clinical trials of its use for treatment of Dravet syndrome,[21,22] a treatment-refractory pediatric epilepsy with high mortality.[4,5] No cases of mitral or aortic valvulopathy were seen in either double-blind clinical trial, but the 16- or 17-week observation period was considered too short to evaluate the cardiovascular safety of fenfluramine. Because of safety concerns based on the past association of fenfluramine with VHD and PAH, when it had been used as a weight loss drug in obese adults at higher doses,[14] an intensive prospective program of regular echocardiographic examinations for patients with Dravet syndrome treated with fenfluramine was instituted for the fenfluramine phase 3 program. This initial interim analysis of echocardiographic results from patients with Dravet syndrome treated for up to 634 days (median = 256 days) with open-label fenfluramine demonstrated that no VHD or PAH was observed in any of the 232 patients. No grade of mitral or aortic valve regurgitation greater than trace was observed at any time. In addition, neither the mean systolic pulmonary artery pressure nor its negligible change from baseline would be considered indicative of PAH. Results of this large study also confirm and reinforce the observations of no VHD or PAH in two small cohorts of patients with Dravet syndrome treated with fenfluramine for up to 30 years.[18-20,23]

Findings regarding lack of VHD and PAH are significant because fenfluramine, which had originally been approved as an anorectic agent to aid in weight loss among obese adults, was reported to be associated with development of both VHD[10] and PAH[17]; reports of this association with increased risk of VHD resulted in its withdrawal from global markets in 1997.[30] Shortly after, a number of studies were published that attempted to estimate the magnitude of the risk of VHD associated with the use of fenfluramine. However, interpretation of these prior studies is confounded by several factors, including lack of baseline echocardiographic assessments, limited accounting for preexisting valve disease risk factors, widely variable study designs, recall bias, unblinded echocardiographic readings, variation in echocardiography machine settings, variation in echocardiographic reading techniques, concomitant use of phentermine,[31] and variation in assessment criteria for pathologic findings.[14,32] Important factors that have been reported to be associated with increased risk of VHD included fenfluramine doses ≥60 mg/day compared with doses <40 mg/day[33] and duration of exposure ≥3 to 6 months.[11-16] Research conducted in the aftermath of the global withdrawal of fenfluramine suggested that the 5HT-2B receptor may have been at least partially involved in the pathophysiologic mechanism(s) responsible for PAH[34,35] and cardiac valvulopathy[36] based primarily on receptor binding assays and cell culture. (+)-Norfenfluramine, the active metabolite of fenfluramine, has been reported to bind to cloned human 5HT-2B receptors with high affinity (K_i = 11 nanomolar) and was shown to be a full agonist with a K_{act} of 18 nmol/L.[36] Nonetheless, despite heightened scientific and clinical interest in understanding a possible causal relationship between these two agents and serious cardiovascular adverse events, neither the absolute risk nor the putative pathophysiology has ever been adequately confirmed with strong supporting scientific evidence.[32]

The present study is the first prospective study of the cardiovascular safety of fenfluramine with well-defined baseline and follow-up echocardiograms in any patient population; it includes the most extensive longitudinal assessment of cardiac valve function and pulmonary artery pressure reported in children and adolescents. Unlike original reports of the association of fenfluramine with VHD (and PAH) in obese adults, echocardiographic assessments were conducted before treatment was initiated in the double-blind clinical trials of fenfluramine in Dravet syndrome, and all patients were absent any degree of aortic or mitral valve regurgitation, including trace, at study start. In addition, any patient with a risk factor for development of VHD or PAH was excluded from participation in the double-blind clinical trials. It is important to note that trace regurgitation is considered to represent normal physiology and is not considered a pathologic finding or a risk factor in current guidelines.[23] All patients underwent regular longitudinal echocardiographic follow-up, and all echocardiograms were obtained via standardized machine settings and a standardized protocol for performing the examination that followed the most recent consensus recommendations on echocardiographic methods for assessing valve function.[23] In addition, cardiologists who interpreted the echocardiograms were blinded to patient information such as patient identification, patient's current dose of fenfluramine in the OLE study, and patient's treatment group in the double-blind clinical trial. With this intensive prospective echocardiographic evaluation, no patient was observed to have developed VHD or PAH during the interim analysis period.

Several factors might have contributed to different cardiovascular findings in the present study in patients with Dravet syndrome compared to previous study findings in obese adults. First, the patient populations are clearly different and likely have differing degrees of risk factors for valvular dysfunction and PAH related to age, treatment history, and comorbidities. Patients in the present study were children and young adults with primarily normal or low normal body mass index (BMI), whereas all patients using

fenfluramine for its anorectic effect were adults, mostly female, and were overweight or obese. Second, patients with Dravet syndrome received fenfluramine at doses up to a maximum of 17 or 26 mg/day (depending on background AED regimen)—doses that were markedly lower than those used for weight loss, for which fenfluramine doses were commonly 60 mg/day and higher.[14] In addition, as noted earlier, patients with a preexisting finding of valvular dysfunction or high pulmonary artery pressure, or any risk factors for VHD or PAH, were excluded from enrollment in the double-blind clinical trials. In the original cohorts of overweight/obese adults treated with fenfluramine, pretreatment echocardiograms were not routinely performed. Hence, the prevalence of preexisting VHD or PAH or of risk factors for their development in those patients was not known.

To our knowledge, the present study also represents the largest study in which serial echocardiograms have been performed on children and young adults (who were treated with fenfluramine). Thus the use of prospective standardized echocardiographic examinations allowed characterization of the natural history of trace regurgitation. A new and unexpected finding in this study was that trace regurgitation was a transient finding, with subsequent echocardiographic examinations reverting to absent or oscillating between absent and trace. Moreover, the point prevalence of trace mitral valve regurgitation and trace aortic valve regurgitation was at all study visits comparable to that reported in normal healthy children by Webb et al, who examined 396 healthy children aged 10-12 years and found trace mitral valve regurgitation in 14.9% of these subjects (95% CI = 11.7%-18.7%).[27] Similarly, Webb et al observed trace aortic valve regurgitation in 2% of subjects in this cohort (95% CI = 1.0%-3.9%). It is important to note that no patient with a finding of trace mitral or aortic regurgitation had a subsequent finding of mild or greater regurgitation during the present study; thus a finding of trace regurgitation was not a precursor for further progression to VHD in the time period of the study. In addition, no differences in the incidence of trace mitral regurgitation were observed for those taking less than or greater than the mean dose studied of 0.41 mg/kg/day, and there were no apparent differences based on the duration of drug exposure.

Observations in this analysis are limited by its open-label design and by the wide variation in duration of exposure to fenfluramine experienced by patients at the time of analysis. Furthermore, quantification of valvular regurgitation was performed through a qualitative assessment and therefore could be subject to some interobserver variability; however, it was performed in accordance with published criteria,[23] and any discrepancies were adjudicated by an experienced cardiologist. In obese adults treated with fenfluramine for weight loss, a treatment duration ≥3-6 months was a risk factor for future cardiac valvulopathy.[11-13,15,16] However, >50% of the patients in the present study have been treated for longer than 6 months without demonstrating any valvulopathy.

5 | CONCLUSIONS

In summary, after a median duration of fenfluramine treatment of 256 days, no VHD or PAH was observed in any of the 232 patients with Dravet syndrome who participated in this program. No effects on ECG parameters of atrioventricular conduction or cardiac depolarization were seen. These results, taken together with the magnitude and durability of the positive effect on seizures previously reported in phase 3 clinical trials in this severe pediatric-onset, refractory epileptic encephalopathy, strongly suggest that significant benefits of fenfluramine for this patient population outweigh potential cardiac risks, which can be monitored via echocardiography. The long-term use of fenfluramine to treat Dravet syndrome and effects of treatment on cardiovascular outcomes will continue to be evaluated.

ACKNOWLEDGMENTS

This study was funded by Zogenix, Inc. (Emeryville, CA, USA). The authors thank ERT/BioMedical Systems and their cardiologists for performing the evaluation of the echocardiograms, and we thank Tim Moore for statistical support. The authors received professional medical writing assistance that was provided by Edward Weselcouch, PhD, of PharmaWrite (Princeton, NJ, USA), and was funded by Zogenix, Inc.

CONFLICT OF INTEREST

WWL received personal fees, research funding, and nonfinancial support from Zogenix, Inc. (Emeryville, CA, USA) during the conduct of the study. BG, GF, and AA received personal fees and own stock/stock options as employees of Zogenix, Inc. PCW received grant/research support from AstraZeneca (Wilmington, DE, USA). MP received personal fees, research funding, and nonfinancial support from Zogenix, Inc., during the conduct of the study. MGK received honoraria for consulting and advisory board services from Zogenix, Inc., and from Brabant Pharma (Manchester, UK). We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

BG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were responsible for acquisition, analysis, and interpretation of data. All authors were responsible for concept and design of the manuscript, participated in all stages of drafting of the manuscript, and critically

revised the manuscript for important intellectual content. All authors approved the final version submitted for publication.

DATA AVAILABILITY STATEMENT

At the current time, Zogenix does not share individual level patient data from our clinical trials.

ORCID

Wyman W. Lai https://orcid.org/0000-0002-9557-1855
Bradley S. Galer https://orcid.org/0000-0002-4735-3327

REFERENCES

1. Campbell JD, Whittington MD, Kim CH, VanderVeen GR, Knupp KG, Gammaitoni A. Assessing the impact of caring for a child with Dravet syndrome: results of a caregiver survey. Epilepsy Behav. 2018;80:152–6.
2. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52(Suppl 2):3–9.
3. Lagae L, Brambilla I, Mingorance A, Gibson E, Battersby A. Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol. 2018;60(1):63–72.
4. Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, *et al*. Mortality in Dravet syndrome. Epilepsy Res. 2016;128:43–7.
5. Shmuely S, Sisodiya SM, Gunning WB, Sander JW, Thijs RD. Mortality in Dravet syndrome: a review. Epilepsy Behav. 2016;64(Pt A):69–74.
6. Jensen MP, Brunklaus A, Dorris L, Zuberi SM, Knupp KG, Galer BS, *et al*. The humanistic and economic burden of Dravet syndrome on caregivers and families: implications for future research. Epilepsy Behav. 2017;70:104–9.
7. Aras LM, Isla J, Mingorance-Le MA. The European patient with Dravet syndrome: results from a parent-reported survey on antiepileptic drug use in the European population with Dravet syndrome. Epilepsy Behav. 2015;44:104–9.
8. Schoonjans A-N, Lagae L, Ceulemans B. Low-dose fenfluramine in the treatment of neurologic disorders: experience in Dravet syndrome. Ther Adv Neurol Disord. 2015;8:328–38.
9. Centers for Disease Control and Prevention (CDC). Cardiac valvulopathy associated with exposure to fenfluramine or dexfenfluramine: U.S. Department of Health and Human Services interim public health recommendations, November 1997. MMWR Morb Mortal Wkly Rep. 1997;46(45):1061–6.
10. Connolly HM, Crary JL, McGoon MD, Hensrud DD, Edwards BS, Edwards WD, *et al*. Valvular heart disease associated with fenfluramine-phentermine. N Engl J Med. 1997;337(9):581–8.
11. Dahl CF, Allen MR, Urie PM, Hopkins PN. Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. BMC Med. 2008;6:34.
12. Hopkins PN, Polukoff GI. Risk of valvular heart disease associated with use of fenfluramine. BMC Cardiovasc Disord. 2003;3:5.
13. Jick H, Vasilakis C, Weinrauch LA, Meier CR, Jick SS, Derby LE. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N Engl J Med. 1998;339(11):719–24.
14. Schoonjans A-S, Marchau F, Paelinck BP, Lagae L, Gammaitoni A, Pringsheim M, *et al*. Cardiovascular safety of low-dose fenfluramine in Dravet syndrome: a review of its benefit-risk profile in a new patient population. Curr Med Res Opin. 2017;33(10):1773–81.
15. Jollis JG, Landolfo CK, Kisslo J, Constantine GD, Davis KD, Ryan T. Fenfluramine and phentermine and cardiovascular findings: effect of treatment duration on prevalence of valve abnormalities. Circulation. 2000;101(17):2071–7.
16. Lepor NE, Gross SB, Daley WL, Samuels BA, Rizzo MJ, Luko SP, *et al*. Dose and duration of fenfluramine-phentermine therapy impacts the risk of significant valvular heart disease. Am J Cardiol. 2000;86(1):107–10.
17. Abenhaim L, Moride Y, Brenot F, Rich S, Benichou J, Kurz X, *et al*. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med. 1996;335(9):609–16.
18. Ceulemans B, Boel M, Leyssens K, Van Rossem C, Neels P, Jorens PG, *et al*. Successful use of fenfluramine as an add-on treatment for Dravet syndrome. Epilepsia. 2012;53(7):1131–9.
19. Ceulemans B, Schoonjans A-S, Marchau F, Paelinck B, Lagae L. Five-year extended follow-up of 10 Dravet patients treated with fenfluramine. Epilepsia. 2016;57(7):e129–e134.
20. Schoonjans A, Paelinck BP, Marchau F, Gunning B, Gammaitoni A, Galer BS, *et al*. Low-dose fenfluramine significantly reduces seizure frequency in Dravet syndrome: a prospective study of a new cohort of patients. Eur J Neurol. 2017;24(2):309–14.
21. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, *et al*. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019;394:2243–54.
22. Nabbout R, Mistry A, Zuberi S, Villeneuve N, Gil-Nagel A, Sanchez-Carpintero R, *et al*. Fenfluramine for treatment-resistant seizures in patients with Dravet syndrome receiving stiripentol-inclusive regimens: a randomized clinical trial. JAMA Neurol. 2019;77(3):300–8.
23. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, *et al*. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2017;30(4):303–71.
24. Boyd B, Smith S, Gammaitoni A, Galer BS, Farfel GM. A phase I, randomized, open-label, single-dose, 3-period crossover study to evaluate the drug-drug interaction between ZX008 (fenfluramine HCl oral solution) and a regimen of stiripentol, clobazam, and valproate in healthy subjects. Int J Clin Pharmacol Ther. 2019;57(1):11–9.
25. Rubino C, Boyd B, Zhang L, Ismail M, Trang M, Farfel G. ZX008 (fenfluramine oral solution) as adjunctive therapy for Dravet syndrome seizures: a pharmacometric approach to quantify potential drug-drug interactions to support phase 3 dose selection. Presented at the 71st Annual Meeting of the American Epilepsy Society; December 1–5, 2017; Washington, DC.
26. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, *et al*. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). Am J Cardiol. 1999;83(6):897–902.
27. Webb RH, Gentles TL, Stirling JW, Lee M, O'Donnell C, Wilson NJ. Valvular regurgitation using portable echocardiography in a healthy student population: implications for rheumatic heart disease screening. J Am Soc Echocardiogr. 2015;28(8):981–8.

28. Jone PN, Ivy DD. Echocardiography in pediatric pulmonary hypertension. Front Pediatr. 2014;2:124.
29. Sheu CF. Regression analysis of correlated binary outcomes. Behav Res Methods Instrum Comput. 2000;32(2):269–73.
30. Onakpoya IJ, Heneghan CJ, Aronson JK. Worldwide withdrawal of medicinal products because of adverse drug reactions: a systematic review and analysis. Crit Rev Toxicol. 2016;46(6):477–89.
31. Fishman AP. Aminorex to fen/phen: an epidemic foretold. Circulation. 1999;99(1):156–61.
32. Weissman NJ. Appetite suppressants and valvular heart disease. Am J Med Sci. 2001;321(4):285–91.
33. Li R, Serdula MK, Williamson DF, Bowman BA, Graham DJ, Green L. Dose-effect of fenfluramine use on the severity of valvular heart disease among fen-phen patients with valvulopathy. Int J Obes Relat Metab Disord. 1999;23(9):926–8.
34. MacLean MMR. The serotonin hypothesis in pulmonary hypertension revisited: targets for novel therapies (2017 Grover Conference Series). Pulm Circ. 2018;8(2):2045894018759125.
35. West JD, Carrier EJ, Bloodworth NC, Schroer AK, Chen P, Ryzhova LM, *et al*. Serotonin 2B receptor antagonism prevents heritable pulmonary arterial hypertension. PLoS One. 2016;11(2):e0148657.
36. Rothman RB, Clark RD, Partilla JS, Baumann MH. (+)-Fenfluramine and its major metabolite, (+)-norfenfluramine, are potent substrates for norepinephrine transporters. J Pharmacol Exp Ther. 2003;305(3):1191–9.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Lai WW, Galer BS, Wong PC, et al. Cardiovascular safety of fenfluramine in the treatment of Dravet syndrome: Analysis of an ongoing long-term open-label safety extension study. *Epilepsia*. 2020;61:2386–2395. https://doi.org/10.1111/epi.16638