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ORIGINAL ARTICLE

An examination of the efficacy and safety of fenfluramine in adults, children, and adolescents with Dravet syndrome in a real-world practice setting: A report from the Fenfluramine European Early Access Program

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Abstract

Objective: To examine the efficacy and safety of fenfluramine in patients with Dravet syndrome (DS) in three age groups: <6, 6-17, and ≥18 years old, treated in a real-world setting.

Methods: Patients with DS were treated with fenfluramine in the European Union Early Access Program (EAP). Following a 28-day baseline period to establish the pretreatment monthly convulsive seizure frequency (MCSF), fenfluramine was started at a dose chosen by the treating physician and gradually titrated based on efficacy and tolerability up to a maximum of 0.7 mg/kg/day.

Seizure incidence was recorded in a written diary, and adverse events (AEs) were reported at each patient visit. Cardiovascular safety was assessed by transthoracic echocardiography before treatment started and at least every 6 months thereafter.
Results: A total of 149 patients have enrolled in the EAP and 63 were <6 years old, 62 were 6-17 years old, and 24 were ≥18 years old. After 3 months of treatment 62%, 53%, and 50% of patients demonstrated ≥75% reduction in MCSF in the <6, 6-17, and ≥18-year-old groups, respectively. This pattern of response was sustained through 12 months of treatment with 55%, 46%, and 80% of the <6, 6-17, and ≥18-year-old groups, respectively, experiencing a ≥75% reduction in MCSF. Most common AEs were loss of appetite (21%) and somnolence (16%). No valvular heart disease or pulmonary artery hypertension was observed.
Significance: The magnitude, consistency, and durability of the response to add-on fenfluramine is consistent across age groups in patients with Dravet syndrome.

KEYWORDS
clinical practice, Dravet syndrome, fenfluramine, refractory epilepsy, seizures

1 | INTRODUCTION

Dravet syndrome (DS) is a rare, severe, pharmacoresistant developmental and epileptic encephalopathy that has its onset during the first year of life.[1] The syndrome is characterized by a high seizure burden, comorbid neurodevelopmental, motor, and behavior problems, decreased quality of life for the patient and caregivers, and an increased risk of premature mortality.[1–4] Although DS is a clinical diagnosis, at least 80% of patients have a pathogenic variant of *SCN1A*, the gene that codes for the alpha-1 subunit of a neuronal voltage-gated sodium channel.[5,6] Treatment with multiple anti-seizure medications (ASMs) is often required, including, for example, valproate, clobazam, topiramate, and stiripentol, but despite this polypharmacy, 45% of patients continue to experience four or more tonic–clonic seizures per month.[7,8] This limited efficacy clearly illustrates the need for new medications and therapies.

Fenfluramine, which acts via agonism of multiple serotonin receptors ($5HT_{1A,\ 2C,\ 2D,\ 4}$) in central serotonergic pathways and through positive modulation of sigma-1 receptors,[9] offers a new therapeutic option with a unique mechanism of action (MOA) for patients with DS. In two randomized, placebo-controlled clinical trials, DS patients whose convulsive seizures were not controlled with their current ASM regimen were treated with fenfluramine added to the ASMs or therapies and demonstrated statistically significant 54% (in patients concomitantly treated with stiripentol) and 65% (in patients not treated with stiripentol) greater reduction in convulsive seizure frequency compared with patients in the placebo groups.[6,10]

Key points

- In the EU Early Access Program, Dravet syndrome patients were treated with fenfluramine in a clinical practice setting
- ≥70% of patients demonstrated at least a 50% reduction in convulsive seizure frequency while treated with fenfluramine for up to 12 months
- The antiseizure response was similar in patients aged <6, 6-18, or ≥18 years
- No incidence of valvular heart disease or pulmonary artery hypertension was observed
- About 50% of patients in each age group discontinued or reduced the dose of an anti-seizure medication while treated with fenfluramine

A similar and durable anti-seizure response has been observed in an open-label extension study in patients who have been treated for up to 3 years.[11] Improvements in everyday executive function assessed with the Behavior Rating Inventory of Executive Function® (BRIEF®) have also been reported in DS patients treated for 1 year with fenfluramine.[12] This beneficial response is potentially a direct effect due to both its unique pharmacology as well as its ability to reduce seizure frequency.

Not all patients with DS had access to or were eligible for participation in the clinical trials of fenfluramine. For patients with long-lasting, seriously debilitating illnesses,

like DS, for whom current treatment options are inadequate, the European Medicines Agency (EMA) may allow compassionate use access to a promising medication that has not yet been authorized for treatment of their condition.[13] Starting in December 2018, Zogenix supported a compassionate use program (also referred to as an expanded access program [EAP]) in the EU for fenfluramine to treat patients with DS prior to its marketing authorization. The EU EAP ended in December 2020, following the approval of fenfluramine for the adjunctive treatment of seizures associated with DS in patients 2 years of age and older, by the EMA.[13]

Preliminary results describing the responses of patients treated in the EU EAP in Italy (n = 52)[14] and Germany (n = 78)[15] have been recently reported. Both analyses reported clinically meaningful reductions in seizure frequency during treatment with fenfluramine and good tolerability of the drug as evidenced by the 85% retention rate in both studies. Here we present a post-hoc secondary analysis focusing on the results in three distinct age groups (children under 6 years old, children 6-17 years old, and adults) using pooled data from the Italian and German EU EAP populations noted above combined with an additional 19 patients from Spain and the United Kingdom.

2 | METHODS

Patients with a clinically confirmed diagnosis of DS, with an unmet medical need (eg, residual seizures or other therapies being contraindicated), and who were not part of a clinical trial were eligible to participate in the EU EAP. Key contraindications for participation in the EAP included hypersensitivity to fenfluramine or any of its excipients, valvular heart disease, pulmonary artery hypertension (PAH), or recent treatment (prior 14 days) with a monoamine oxidase inhibitor.

Data collection and analysis were approved by ethics committees in each country, and anonymized data were pooled for analysis. Fenfluramine HCl oral solution (2.2 mg/mL fenfluramine) was provided to patients by Zogenix, Inc. (PCI Pharma Services). Treatment with fenfluramine was added to each patient's ASM regimen following a 28-day baseline period to establish the pretreatment monthly convulsive seizure frequency (MCSF). The number of each patient's ASMs remained unchanged during the baseline period, but the ASM regimens could be adjusted at the treating physician's discretion throughout follow-up during treatment with fenfluramine.

Convulsive seizures included hemiclonic, tonic, clonic, generalized tonic–clonic, and focal with clearly observable motor signs. Fenfluramine treatment added to each patient's current ASM or treatment regimen was initiated at a dose chosen by the treating physician and gradually titrated based on efficacy and tolerability. The maximum allowed dose was 0.7 mg/kg/day (absolute maximum of 26 mg/day) in patients not concomitantly treated with stiripentol or 0.4 mg/kg/day (absolute maximum of 17 mg/day) in patients receiving stiripentol. All daily doses were administered in two equal doses delivered about 12 hours apart.

During participation in the EU EAP, caregivers recorded the incidence of all seizures in a written diary. Patients were typically seen every 3 or 6 months, and caregivers were asked about adverse events (AEs) during those visits. Other information recorded at the visits included fenfluramine treatment details (including fenfluramine discontinuation) and changes in ASM regimen (ie, changes in dosing, discontinuation of ASMs, or addition of new ASMs). AEs were reported to the regulatory authorities and to the sponsor. Echocardiograms were conducted prior to initiating fenfluramine and at least every 6 months thereafter to assess cardiac valve function and pulmonary artery pressure. A pulmonary artery pressure ≥35 mm Hg was considered evidence of possible PAH.

Anonymized, individual-level data of patients treated with fenfluramine in 17 European centers were merged into a single dataset. Data were extracted from patient charts and seizure diaries at baseline and each visit (at 3, 6, and 12 months). Some data included in the pooled analysis have been previously published.[14,15] No imputation of missing data was performed.

2.1 | Data analysis

In this pooled analysis, anti-seizure response was compared to baseline and categorized as the proportion of patients exceeding the following thresholds for reduction in MCSF: >25%, >50%, >75%, or 100% reduction. The anti-seizure response was summarized after 3, 6, and 12 months in each age group.

At the most recent patient visit physicians completed the Clinical Global Impression (CGI) instrument for each patient. The CGI is used to rate the overall change during treatment with fenfluramine on a 7-point scale ranging from 7, "very much improved," to 1, "very much worse." Patients rated 6 or 7 on the CGI scale were considered to have had a clinically meaningful outcome. No formal statistical analysis was conducted, primarily due to the imbalance in the number of patients in each age group. Continuous variables are presented as mean ± SD unless otherwise noted.

3 | RESULTS

A total of 149 patients were enrolled as of the cutoff date of March 2021 for this analysis. The baseline characteristics of the entire analysis population and the patients in each age group are presented in Table 1. The mean age of DS onset was 5.9 ± 3.1 months, and 97% of patients had a pathogenic variant of *SCN1A*. Nearly all patients were treated concomitantly with three or more ASMs, and more than half were concomitantly treated with stiripentol. A total of 13 patients were also treated with cannabidiol.

The mean age at initiation of fenfluramine treatment was 10.2 ± 8.9 years, with two patients <2 years old (age range at initiation was 1-46 years). The median duration of treatment with fenfluramine for the entire analysis population was 11.3 months (range, 1-22.9 months), which was similar among the age groups (Table 2). Titration to the final dose occurred over a median 28, 30, and 21 days in the <6, 6-17, and ≥18-year-old groups, respectively (Table 2). At the time of this analysis, 138 patients (93%) had been treated for at least 3 months, 118 (79%) for at least 6 months, and 80 (54%) for at least 12 months. The reduction in the number of patients with longer follow-up times was primarily due to staggered entry into the EAP and not to withdrawal from the program. The mean dose of fenfluramine in the entire analysis population at the most recent follow-up was 0.39 ± 0.15 mg/kg/day, and at the most recent patient visit, was similar in patients treated with or without stiripentol. Eighteen patients (12%) withdrew from fenfluramine treatment, with the primary reasons cited being lack of efficacy (n = 13, 9%) and adverse events (n = 3, 2%).

3.1 | Efficacy

Figure 1 shows the responder results for each age group and treatment duration. The patterns of responses were similar in each age group at each treatment duration. Overall, more than half of all patients experienced a profound reduction (ie, >75% reduction) in MCSF. In the entire analysis population, the anti-seizure responses were similar in patients also receiving stiripentol and those who did not. For example, after 3 months of treatment, 73% of the group treated with stiripentol demonstrated a ≥50% reduction in convulsive seizure frequency, compared with 84% in the group not treated with stiripentol. The ≥75% responder rates in these two groups of patients were 54% and 60%, respectively. In the patients also receiving cannabidiol, 11 of 13 (85%) demonstrated a ≥50% reduction in convulsive seizure frequency and four of 13 (31%) demonstrated a ≥75% reduction in convulsive seizure frequency. An indirect indicator of effectiveness is shown by the fact that, overall, 51% of patients were able to either reduce the dose or discontinue a concomitant ASM after the addition of fenfluramine (21% reduced dose of ASM, 30% discontinued ASM). The proportion of patients was similar across the age groups with 51%, 52%, and 50% able to reduce dose or discontinue ASM in the <6, 6-17, and ≥18-year-old groups, respectively.

The physician-rated CGI is presented in Figure 2. In the overall population, 61.5% of patients were rated as "much improved" or "very much improved" by their physician (ie, a clinically meaningful improvement). The proportion of patients <6, 6-17, and ≥18 years old who experienced a clinically meaningful improvement based on CGI ratings during treatment with fenfluramine was similar in each age group: 69.8%, 55.8%, and 54.1%, respectively.

3.2 | Safety

A summary of adverse events is presented in Table 3. Overall, 47% of patients experienced one or more AEs, with the incidence ranging from 35% in the <6-year-old group to 63% in the ≥18-year-old group. Loss of appetite (n = 31, 21%) and somnolence (n = 24, 16%) were the two

TABLE 1 Baseline characteristics of analysis population

	Age group			
	<6 years n = 63	**6-17 years n = 62**	**≥18 years n = 24**	**All patients N = 149**
Sex, M:F (M%:F%)	34:29 (54%:46%)	27:35 (44%:56%)	14:10 (58%:42%)	75:74 (50%:50%)
SCN1A mutation	98%	95%	96%	97%
Age at epilepsy onset, months, mean ± SD	6.0 ± 3.5	5.5 ± 2.3	6.4 ± 3.5	5.9 ± 3.1
Duration of disease, years, mean ± SD	4.1 ± 2.4	10.6 ± 3.2	26.1 ± 9.1	10.2 ± 8.9
At least 1 comorbidity, %	90%	97%	100%	95%
Moderate or severe intellectual disability, %	32%	68%	79%	55%
≥3 Anti-seizure medications, %	73%	69%	75%	72%
Stiripentol comedication, %	57%	60%	42%	56%

TABLE 2 Summary of fenfluramine dosing

	Age group			
	<6 years n = 63	**6-17 years n = 62**	**≥18 years n = 24**	**All patients N = 149**
Age at start of fenfluramine, years, mean ± SD (median [min, max])	3.6 ± 1.3 (4.0 [1, 5])	10.6 ± 3.1 (11 [6, 17]	26.6 ± 8.9 (28 [18, 46])	10.2 ± 8.9 (7.2 [1, 46])
Dose at last follow-up, mg/kg/day, mean ± SD	0.42 ± 0.15	0.38 ± 0.14	0.31 ± 0.15	0.39 ± 0.15
Maximum dose, mg/kg/day, mean ± SD	0.49 ± 0.16	0.42 ± 0.16	0.31 ± 0.14	0.43 ± 0.17
Duration of titration, days, median (min, max)	28 (7, 450)	30 (4, 450)	21 (7, 630)	28 (4, 630)
Duration of treatment, months, median (min, max)	10.3 (1.0, 19.1)	11.7 (1.1, 22.4)	11.5 (2.8, 22.9)	11.3 (1.0, 22.9)
Patients stopping fenfluramine, %	7.9%	17.7%	8.3%	12.1%

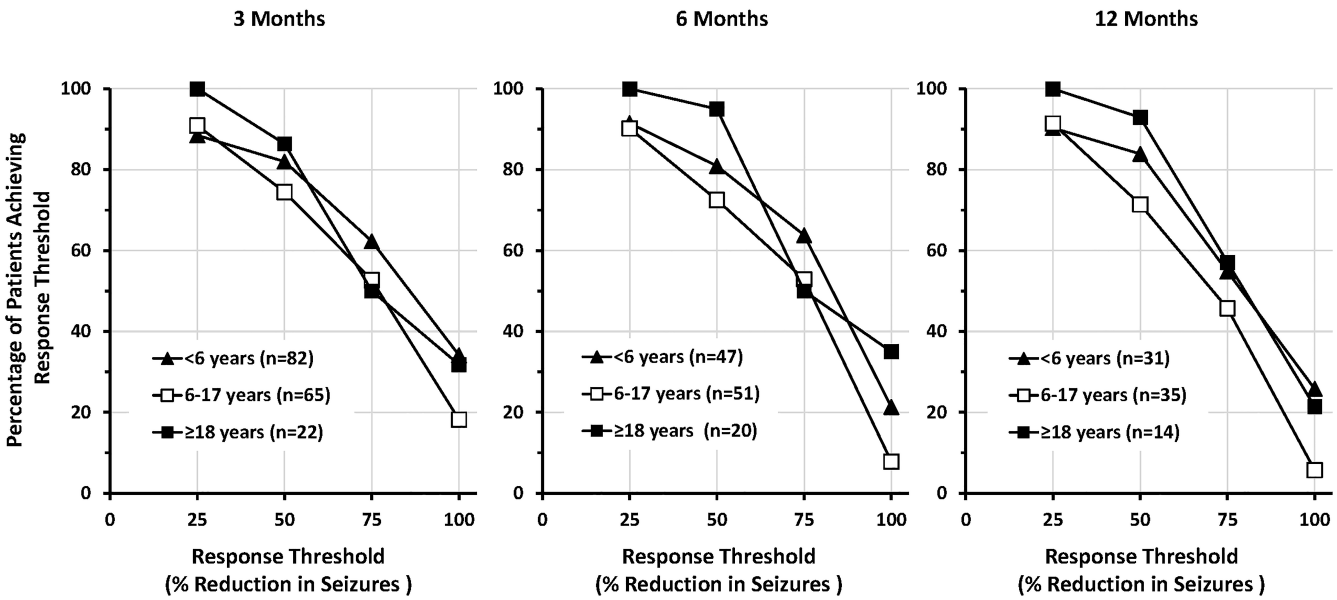

FIGURE 1 Anti-seizure efficacy of fenfluramine in patients with Dravet syndrome in three different age groups over 3, 6, and 12 months of treatment

most common adverse events reported in ≥10% of patients. The incidence rates of AEs were similar in patients receiving stiripentol and/or cannabidiol compared with those who were not receiving these drugs. One serious AE was observed in the <6-year-old group. This child discontinued fenfluramine after about 3 months of treatment at 0.5 mg/kg/day primarily due to poor efficacy and following several critical multi-day convulsive episodes, including one requiring hospitalization. After fenfluramine discontinuation, additional similar episodes occurred that were considered as an expression of a severe form of DS and not secondary to drug-induced seizure worsening. During follow-up, fenfluramine was re-introduced, resulting in a 50% reduction in seizure frequency relative to the pre-treatment period and to the 2-month period in which the patient was without the drug. This benefit was maintained during the 20 months following re-introduction.

Transthoracic echocardiographic examinations were regularly performed in all patients according to EMA recommendations and revealed no incidence of valvular heart disease or PAH in any patient during the analysis period. No cases of sudden unexpected death in epilepsy (SUDEP) or other premature mortality occurred during the EU EAP.

4 | DISCUSSION

In phase 3 clinical trials, fenfluramine use produced durable, clinically meaningful levels of seizure frequency

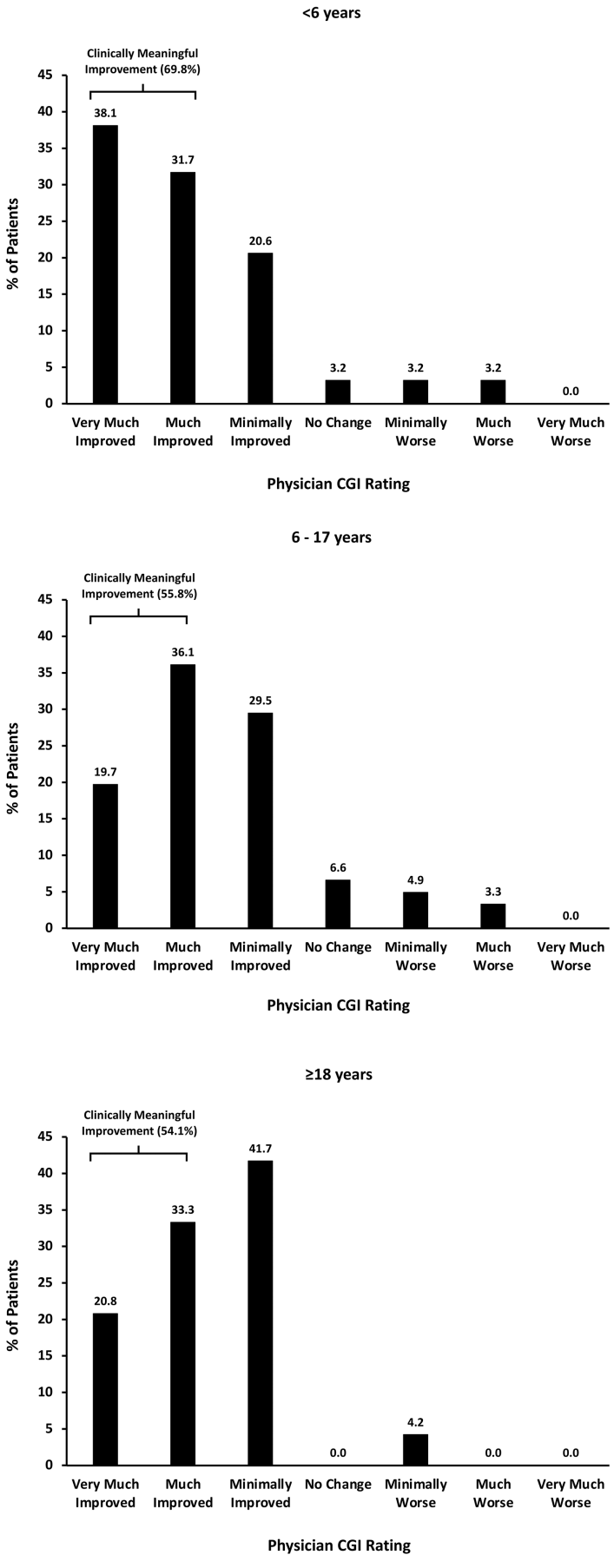

FIGURE 2 Physician-rated clinical global impression

	Age group			
	<6 years n = 63	6-17 years n = 62	≥18 years n = 24	All patients N = 149
Any AE	22 (35%)	33 (53%)	15 (63%)	70 (47%)
Loss of appetite	11 (17%)	12 (19%)	8 (33%)	31 (21%)
Somnolence	7 (11%)	14 (23%)	3 (13%)	24 (16%)
Psychiatric/behavioral AE	1 (2%)	7 (11%)	5 (21%)	13 (9%)
Ataxia/gait disturbance	3 (5%)	3 (5%)	0	6 (4%)
Sleep disturbances	3 (5%)	2 (3%)	1 (4%)	6 (4%)

Note: Incidence is number of patients (% or patients).

Abbreviation: AE, adverse event.

TABLE 3 Summary of adverse events reported by ≥5% of patients in any age group during treatment with fenfluramine.

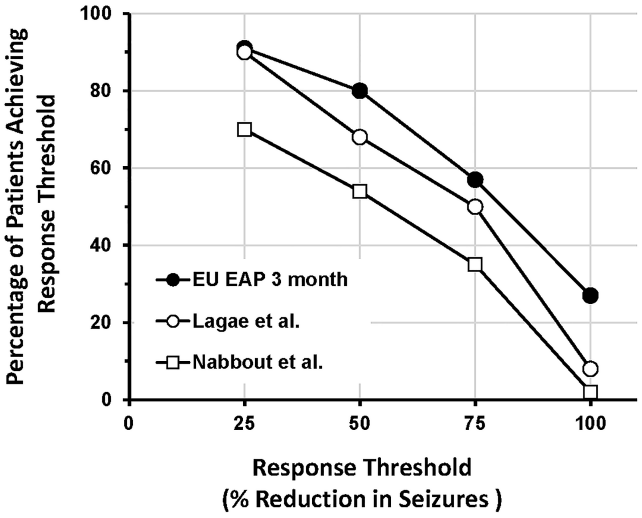

FIGURE 3 Comparison of responder rates in the EU EAP with the phase 3 studies of fenfluramine. The 3-month time point in the EU EAP was chosen because it closely approximates the duration of treatment (titration plus maintenance periods) used in the phase 3 clinical trials (Lagae et al[6]; Nabbout et al[10]).

reduction in DS patients for up to 3 years, with a similar efficacy and safety profile in patients 2-6 years old and those patients 6-18 years old when starting treatment with fenfluramine.[6,10,16] The present study represents the first opportunity to evaluate fenfluramine in a real world setting to examine the relative efficacy and safety across various age groups, including adults who were not included in the original Phase 3 trials. In addition, the results of the present analysis suggest that this same level of benefit observed in the randomized, placebo-controlled clinical trials translates to the real-world practice setting, as the majority of patients experienced robust reductions in convulsive seizure frequency with consequent reduction or discontinuation of other ASMs with maintenance of seizure control. As shown in Figure 3, the responder rates observed in the EU EAP after 3 months of treatment were similar to those seen in the phase 3 clinical trials (which had 14-15 weeks' duration of treatment). In Study 1, a randomized, double-blind, placebo-controlled clinical trial in which patients treated with concomitant stiripentol were excluded, 68% of patients treated with 0.7 mg/kg/day fenfluramine experienced ≥50% reduction in convulsive seizure frequency over the combined 14-week titration and maintenance periods.[6] In Study 2, in which all patients were required to be concomitantly treated with stiripentol during the combined 15-week titration and maintenance periods, the 50% responder rate reached 54%.[10] In the present analysis, about 80% of all patients demonstrated this level of anti-seizure effectiveness and the response was similar in each age group. Tolerability of fenfluramine was indicated by the fact that only 12% of patients withdrew from fenfluramine treatment in the EAP. This withdrawal rate compares favorably with the experience in the phase 3 clinical trials in which 6%-16% of patients treated with the most effective doses of fenfluramine withdrew prior to completion of the protocol.[6,10,16]

This EU EAP analysis provides additional evidence of the effectiveness of fenfluramine in adult patients and shows that the response in this older group is similar to that observed in the younger groups of patients. As illustrated in Figure 1, the responder profile in the adult group is nearly identical to those observed in the other age groups, both in the large percentage of responders and the durability of the response through 12 months. Similarly, the CGI physician assessments of the changes in the adult patients were similar to the ratings in the younger patients. A total of 54% of adult patients were rated as much or very much improved compared with 56% or 70% in the 6-17 and <6-year-old groups, respectively.

Unlike the phase 3 clinical trials which required the patients to remain on a stable ASM treatment regimen during the study, the use of fenfluramine in the EU EAP

was instead treated as clinical practice and physicians could adjust their patient's ASM regimen. Overall, about 50% of patients were able to reduce their ASM burden, with 30% able to completely eliminate one or more ASMs from their treatment regimen without having an apparent effect on the anti-seizure response to fenfluramine. These changes were similar in each of the age groups of patients. This observation may be important for patients with DS because some of the ASMs used in its treatment may contribute to cognitive dysfunction,[17] and reducing doses or eliminating the drugs from the treatment regimens may have a positive influence on long-term cognitive function and in reducing the possibility of drug–drug interactions.

The ability of fenfluramine to consistently get patients to 50% or 75% reduction in MCSF has potential implications for other long-term patient outcomes, for example, SUDEP and delays of neurodevelopmental outcome. A recent analysis of SUDEP incidence in 732 DS patients treated with fenfluramine, representing 1185 person-years of observation, reported an all-cause mortality and SUDEP incident rate of 1.7 per 1000 person-years (95% CI, 0.4-6.7), a value considerably lower than those reported by Cooper and colleagues for a cohort of DS patients receiving standard of care (all-cause: 15.8 per 1000 person-years [95% CI, 9.9-25.4], and SUDEP: 9.3 per 1000 person-years [95% CI, 5.0-17.3]).[2,18] Additionally, DS patients treated with fenfluramine who experienced ≥50% reduction in MCSF during at least 1 year of treatment were significantly more likely to experience clinically meaningful improvement in aspects of executive function compared with patients not reaching this seizure response threshold.[12]

Given the cardiovascular safety history of fenfluramine when used at doses of 60 to 120 mg/day or more to treat adult obesity (for review, see Schoonjans et al[19]), an extensive cardiovascular safety monitoring program was implemented in the fenfluramine phase 3 development program for the treatment of DS in which there were no observations of cardiac valvular heart disease or PAH in any patient at any time.[20] Likewise, in our EU EAP program, patients were also monitored with periodic echocardiography, and to date, no echocardiographic evidence of valvular heart disease or PAH has been observed. Lastly, the same holds true for the two cohorts of Belgian patients with DS that have now been treated with fenfluramine for up to 35 years.[19] The overall exposure to fenfluramine in these studies of DS patients was about 1095 person-years.[18]

4.1 | Limitations

Conclusions about the efficacy and tolerability of fenfluramine in the EU EAP are based on observations of the drug responses in clinical practice; however, the efficacy and tolerability observed in our real-world cohort closely mimics what was seen in the more rigorous, placebo-controlled phase 3 studies, as well as the open-label extension of those studies. Because the EU EAP was based on clinical practice, not all centers collected data on seizure types, and, therefore, analysis of the effect of fenfluramine on the frequency of individual seizure types was not possible. The CGI instrument requires a comparison to the baseline condition of the patient and thus may be subjected to recall bias.

5 | CLINICAL RELEVANCE

The magnitude, consistency, and durability of response to FFA for the treatment of seizures associated with DS were similar in patients with DS regardless of age group. The present study suggests that benefits observed in the phase 3 program carry over when the product is used in real-world clinical practice. Additionally, these data demonstrate that the effects of fenfluramine when used to treat adult patients with DS were virtually identical to those observed in the younger patient groups. Finally, about 50% of patients were able to reduce doses or eliminate one or more ASMs during this analysis, while maintaining high levels of seizure-frequency reduction, suggesting that fenfluramine may represent a first-line treatment for this devastating epileptic syndrome.

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CONFLICT OF INTEREST

RG reports research grants from Zogenix during conduct of the submitted work; speaking/consulting for Zogenix outside the submitted work; being an investigator for studies with Biocodex, UCB, Angelini, and Eisai Inc.; and serving on speaker/advisory boards for Biocodex, Novartis, BioMarin, and GW Pharma outside the submitted work. NS has served on scientific advisory boards for Zogenix, GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Zogenix, Eisai, BioMarin, Livanova, and Sanofi; and has served as an investigator for Zogenix, Marinus, BioMarin, UCB, and Roche. AA-S received funding for research and educational activities from Zogenix, GW, UCB, Bial, Eisai, Sanofi, Neuraxpharm, and Arvelle. MP reports a research grant from Zogenix, Inc. FD reports research funding from Zogenix. TM reports research funding from Bial, Eisai, GW Pharma, UCB Pharma, and Zogenix. AG-N reports personal fees or research grants from Arvelle Therapeutics, Bial, Biocodex, Eisai, Esteve, GW Pharma, PTC Therapeutics, Sanofi, Stoke, UCB, and Zogenix. TP reports research funding from Zogenix; and consulting and speaking for Desitin, Shire, Novartis, UCB Pharma, and Zogenix. SMZ reports research support from Epilepsy Research UK, Dravet Syndrome UK, and Zogenix; consultancy, advisory, and speaker support for GW Pharma, Encoded Therapeutics, Stoke Therapeutics, Eisai, UCB Pharma, Jaguar Gene Therapy, Arvelle, and Zogenix. AL is an employee of, and has ownership interest in, Zogenix. AGammaitoni is an employee of, and has ownership interest in, Zogenix, Inc. AS reports personal fees and grants from Angelini Pharma/Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Marinus Pharma, UCB, UNEEG medical, and Zogenix. 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.

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