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## FULL-LENGTH ORIGINAL RESEARCH

# Efficacy, tolerability, and retention of fenfluramine for the treatment of seizures in patients with Dravet syndrome: Compassionate use program in Germany

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## Abstract

**Objective:** Dravet syndrome (DS) is a rare but severe drug-resistant epilepsy. Before the approval of fenfluramine (FFA) for the treatment of seizures in DS, patients in Germany could receive treatment under a compassionate use program (CUP).

**Methods:** We conducted a multicenter, retrospective, observational study to describe the efficacy, tolerability, and retention of FFA within the CUP. Patients received add-on therapy with oral FFA gradually titrated to a target dose between .13 and .7 mg/kg/day.

**Results:** Overall, 78 patients with DS (median age = 8.0 years, range = 2.1–46.0; 53% female, median concomitant antiseizure medications [ASMs] = 3) were treated with FFA for a median duration of 255.5 days (range = 31–572). Responder rates

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(a  $\geq 50\%$  reduction;  $n = 78$ ) and seizure-freedom rates at 3 months were 68% and 14% for total seizures, respectively, and 67% and 23% for generalized tonic-clonic seizures. Responder rates were consistent at 6 and 12 months ( $n = 66$  and  $n = 43$ , respectively). Median seizure days per month significantly decreased from 10.0 (range = .5–30) to 3.0 (range = 0–30) in the 3-month period before and after FFA treatment ( $p < .001$ ). Significantly fewer patients reported at least one episode of status epilepticus (28% vs. 14% patients before and after FFA initiation,  $p = .005$ ). During FFA treatment, 35 (45%) patients were able to discontinue a concomitant ASM. At the last follow-up date, 66 (85%) patients remained on treatment with FFA. The most common adverse events were somnolence (36%), decreased appetite (22%), and ataxia (8%). Forty-eight (62%) patients were reported as having a meaningful global clinical improvement.

**Significance:** In a large cohort of patients, FFA demonstrated efficacy across a range of outcomes including clinically significant reductions in convulsive seizures, and was well tolerated, providing valuable information for real-world practice.

#### KEYWORDS

Clinical Global Impression of Change, convulsive seizures, Dravet syndrome, fenfluramine, real-world, status epilepticus

## 1 | INTRODUCTION

Dravet syndrome (DS) is a rare genetic disorder predominantly caused by mutations in the *SCN1A* gene, characterized by severe, drug-resistant epilepsy and varying degrees of cognitive and behavioral impairment.<sup>1</sup> The disorder typically begins in infancy with tonic-clonic or clonic febrile seizures in the first year of life, with subsequent development of afebrile seizure types including myoclonic seizures, atypical absences, and focal seizures between the ages of 6 months and 2 years.<sup>1</sup> The majority of patients experience episodes of status epilepticus (SE), a manifestation that requires emergency medical attention and that can result in worse outcomes, including death.<sup>2,3</sup>

The treatments used for DS are intended to reduce the seizure burden.<sup>1</sup> The antiseizure medications (ASMs) valproate and clobazam (CLB) are the first-line treatments; however, the majority of patients continue to have seizures that are poorly controlled.<sup>1</sup> Fenfluramine (FFA), the most recent addition to the treatment armamentarium, was approved in 2020 in the United States and the European Union (EU) as an adjunctive therapy for seizures in DS patients from the age of 2 years. Other adjunctive treatments include stiripentol (STP), approved in the EU in 2007 and the United States in 2018, and cannabidiol (CBD), approved in the United States and EU in 2018 and 2019.<sup>1,4</sup> In addition, other ASMs including bromides,

#### Key Points

- Seventy-eight patients with Dravet syndrome were treated with FFA at multiple centers within the CUP in Germany
- FFA had a good retention rate over a sustained period; 85% of patients remained on treatment with FFA for a median duration of 255.5 days
- FFA was associated with clinically meaningful reductions in total and convulsive seizures, seizure days per month, and episodes of status epilepticus
- FFA was associated with reductions in the number or dose of concomitant antiseizure medications in 68% of patients
- FFA was well tolerated, with the main adverse events being somnolence (36%), decreased appetite (22%), and ataxia (8%)

topiramate (TPM), and levetiracetam (LEV) are also used to reduce seizures in patients with DS.<sup>1,4</sup>

The mechanism by which FFA exerts its antiseizure properties is still being elucidated; available data show it may act through serotonin and sigma-1 receptors.<sup>5</sup> FFA has been shown to be efficacious with a good tolerability

profile in Phase III randomized controlled trials (RCTs) in patients with DS with seizures not controlled by current ASMs.<sup>6,7</sup> FFA was evaluated at a dose of .2 mg/kg/day or .7 mg/kg/day in the first trials,<sup>6</sup> followed by another trial with comedication with STP as a precondition that required a lower dose of FFA due to its interaction with STP (.4 mg/kg/day).<sup>7</sup> In both trials, adjunctive treatment with FFA was associated with significant reductions in convulsive seizure frequency compared to placebo together with significant increases in seizure-free intervals.<sup>6,7</sup> In an open-label extension (OLE) of these trials, FFA demonstrated continued clinically meaningful reductions in convulsive seizure frequency up to a median duration of treatment of 631 days.<sup>8–10</sup> In addition, the RCTs and the OLE study have shown that FFA is generally well tolerated. The long-term efficacy and safety have also been demonstrated by follow-up data from the first prospective study for the DS indication that was conducted in Belgium encompassing a mean treatment duration of 16.1 (range = 6–27) years; over a 5-year period in 10 patients, four patients had seizure-free intervals of at least 2 years and an additional three were seizure-free for the entire period.<sup>11,12</sup> Of note, FFA had previously been used for weight loss in obese adults, but was withdrawn from the market in 1997 due to reports of cardiac valvulopathy and pulmonary arterial hypertension (PAH) in patients treated with high doses of FFA in combination with phentermine.<sup>13</sup> Although the dose of FFA used in patients with DS is substantially lower, the assessment of cardiovascular safety is an important consideration.

There have been limited data regarding the benefits of FFA in DS outside of clinical trials, especially with regard to the modern treatment pathway including use of STP.<sup>14</sup> EU regulations for compassionate use allow access to investigational products prior to their approval to patients with a high unmet need outside a clinical trial setting.<sup>15</sup> As such, prior to its approval in the EU, FFA was made available by the pharmaceutical company Zogenix as part of a compassionate use program (CUP; also known as an expanded access program [EAP]). Data from patients treated within a CUP may be more reflective of clinical experience in a real-life setting and as such are a useful addition to the evidence base. Specchio et al.<sup>16</sup> have recently reported on the CUP experience in Italy in 52 patients with DS treated with add-on FFA. Here, we report the results from the FFA CUP in 78 patients with DS in Germany, providing further evidence supporting the use of FFA in a real-world setting across a range of efficacy outcomes. In particular, this study examines the temporal evolution of seizures and SE burden, the concomitant ASM drug load, the change in the clinical global impression, and the evaluation of safety including cardiac monitoring.

## 2 | MATERIALS AND METHODS

### 2.1 | Patients and study design

This was a retrospective study of patients with DS in the FFA CUP who attended the epilepsy clinics in Bielefeld, Erlangen, Freiburg im Breisgau, Frankfurt am Main, Giessen, Kiel, Radeberg (near Dresden), Tübingen, and Vogtareuth (near Munich). In Germany, treatment with FFA was provided by Zogenix to patients with DS within the CUP from March 2019 until February 2021. Inclusion criteria to participate in the CUP included having a clinical diagnosis of DS and no echocardiographic signs of cardiac valve dysfunction and pulmonary arterial hypertension. Patients received an oral solution of 2.2 mg/ml FFA base twice daily with a gradual titration to a maximum dose of .7 mg/kg/day or 26 mg/day. In patients taking concomitant STP, titration of FFA was possible up to .4 mg/kg/day or 17 mg/day. The study received approval from the ethics committee of the University of Frankfurt. As this was a retrospective study, informed consent was not required. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed.<sup>17</sup>

### 2.2 | Data collection

All patients who started FFA between March 2019 and November 2020 and had taken at least one dose of FFA were included in this study. Patients were typically seen every 3 to 6 months. Data were obtained from patient case notes or seizure diaries, including patient demographics, clinical features, treatment details, and efficacy outcome measures. Treatment details included prior ASMs, concomitant ASMs at baseline and during treatment with FFA, dosage of FFA (initial, target, and at last follow-up), length of exposure to FFA, adverse events (AEs), and treatment discontinuations. Patients were asked about the occurrence of AEs at each visit, and AEs were documented according to World Health Organization criteria. Echocardiograms were conducted every 6 months. In accordance with the protocol, AEs were reported to the regulatory authorities.

Efficacy outcome measures included responder rates (reductions in total seizures and generalized tonic-clonic seizures [GTCSSs] from baseline), seizure-free status, number of seizure days per month, episodes of SE, the Clinical Global Impression of Change (CGIC), impact of FFA on concomitant ASM consumption, and the retention time on FFA. Seizures and SE were defined according to the International League Against Epilepsy.<sup>18–20</sup> The CGIC was administered at the last follow-up visit, whereby clinicians, who are experts in the disease area and were trained in the use of the CGIC,

rated the changes in functioning during treatment from much worse to very much improved on a 6-point categorical rating scale. The numbers of monthly seizures and seizure days (documented each month or as a monthly average since the previous 3-month review by the clinician) were obtained from case notes or seizure diaries if available. To evaluate the responder rates, reductions in the frequency of seizures of  $\geq 25\%$ ,  $\geq 50\%$ ,  $\geq 75\%$ , and 100% (seizure-free) during follow-up were compared to the 3-month baseline. The percentage of patients with an increase ( $\geq 25\%$ ) or no change ( $\geq 0\%$  and  $< 25\%$ ) in seizure frequency was also documented. Response rates were determined for the first 3 months in all patients who were treated with FFA, and for patients with a minimum of 6 months and 12 months of follow-up. An intention-to-treat approach was utilized, whereby data were analyzed for all patients reaching 3, 6, and 12 months; last observation carried forward was not used.

## 2.3 | Statistical analysis

Descriptive analysis was performed on the data using SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA). Continuous data are presented as the mean, SD, median, and range and categorical variables as frequencies and percentages. The difference in the median seizure days per month in the 3-months before and the last 3-months of FFA treatment was analyzed using the Wilcoxon signed-rank test. A Pearson chi-squared test was used to examine the difference in the percentage of patients who experienced at least one episode of SE before and after treatment with FFA (episodes that occurred in the 6 months prior to FFA treatment vs. episodes occurring in the entire FFA treatment period). Retention time on FFA was estimated using Kaplan–Meier survival curves, and comparisons were performed using the log-rank test for adults versus children.

## 3 | RESULTS

### 3.1 | Patients

Seventy-eight patients with DS were treated with FFA in the CUP. The treatment duration ranged from 31 days to 572 days (mean [SD] = 278 [155.9], median = 255.5 days), equivalent to a total of 59.4 patient-years of exposure. At the last follow-up date in February 2021, 66 (85%) patients remained on treatment with FFA; 12 patients discontinued treatment due to either lack of efficacy ( $n = 8$ ) or an AE ( $n = 4$ ).

The baseline demographic and clinical characteristics are shown in Table 1. Overall, 41 patients (53%) were female, and the median age at the start of treatment with FFA was 8.0 years (range = 2.1–46.0). Genetic analysis

showed a *SCN1A* gene variation in 73 (94%) patients, and in five patients diagnosis of DS was based on the clinical presentation. Severe, moderate, or mild degree of cognitive impairment, as assessed by the physician, was reported in the vast majority of patients.

At baseline, patients were being treated with a median of 3.0 ASMs (range = 1–5), most commonly valproic acid (VPA;  $n = 48$ , 62%), CLB ( $n = 45$ , 58%), STP ( $n = 38$ , 49%), and bromide ( $n = 35$ , 45%); 10 patients (13%) were being treated with CBD. Furthermore, four (5%) patients were on the ketogenic diet and three (4%) were being treated with vagus nerve stimulation therapy. In the past, patients had previously failed a median of three ASMs (range = 0–13, not including current ASMs), most commonly LEV ( $n = 49$ , 63%), VPA ( $n = 27$ , 35%), TPM ( $n = 27$ , 35%), and STP ( $n = 24$ , 31%; Table S1). In addition, 17 (22%) patients had previously been on the ketogenic diet.

Onset of seizures was at between 2 and 12 months of age for all patients except in one patient with an onset at 30 months (mean [SD] = 6.1 [3.9] months; Table 1). In the 6 months prior to the start of FFA treatment, 76 (97%) patients had had at least one GTCS; myoclonic seizures and focal seizures were each reported in 42 (54%) patients, and absence seizures and drop seizures occurred in 34 (44%) and 33 (42%) patients, respectively (Table 1). Episodes of SE were common, with 65 (83%) patients having experienced at least one episode in their lifetime.

### 3.2 | Treatment with FFA

The initial dose of FFA base ranged from .03 to .28 mg/kg/day (mean [SD] = .12 [.05], median = .10 mg/kg/day; median daily dosage = 3.5 mg, range = .4–13). The first target dose was reached within a median of 28.0 days (range = 4–210), and it varied from .13 to .70 mg/kg/day (mean [SD] = .38 [.16], median = .35 mg/kg/day; median daily dosage = 10.8 mg, range = 1.7–26). At the last follow-up (median = 255.5 days), the dose of FFA ranged from .10 mg/kg/day to .77 mg/kg/day (mean [SD] = .40 [.19], median = .38 mg/kg/day; median daily dosage = 11 mg, range = 1.7–26). Of note, the dose per kilogram bodyweight was marginally higher than the recommended maximum dose of .7 mg/kg/day in five children due to them losing weight during treatment.

### 3.3 | Clinical outcomes

#### 3.3.1 | Seizures

Responder rates over time for total seizures and GTCS are shown in Figure 1 and Table S2. At 3 months of treatment

**TABLE 1** Patient characteristics at baseline

Characteristic	Value
Patients	78
Sex, <i>n</i> (%)	
Female	41 (53)
Male	37 (47)
Age at epilepsy onset, months, mean (SD); median (range)	6.1 (3.9); 5.8 (2.0–30.0)
Age at start of FFA treatment, years, mean (SD); median (range)	10.9 (9.4); 8.0 (2.1–46.0)
Bodyweight, kg, mean (SD)	33.9 (20.0)
SCN1A variation, <i>n</i> (%)	73 (94)
Prior and concomitant ASMs	
Prior ASMs, <i>n</i> , median (range)	3.0 (0–13)
Concomitant ASMs, <i>n</i> , median (range)	3.0 (1–5)
Concomitant ASMs, <i>n</i> (%)	
1	8 (10)
2	17 (22)
3	34 (44)
4	17 (22)
5	2 (3)
Most common concomitant ASMs, <i>n</i> (%)	
VPA	48 (62)
CLB	45 (58)
STP	38 (49)
Br	35 (45)
TPM	17 (22)
CBD	10 (13)
BRV	6 (8)
LEV	5 (6)
Seizures	
Seizure type <sup>a</sup> , <i>n</i> (%)	
GTCS	76 (97)
Myoclonic	42 (54)
Focal	42 (54)
Absence	34 (44)
Drop seizures	33 (42)
Seizure days per month, mean (SD); median (range) <sup>b</sup>	13.0 (9.2); 10.0 (.5–30)
Status epilepticus	
Status epilepticus, <i>n</i> (%) <sup>a</sup>	22 (28)
Status epilepticus life-time prevalence, <i>n</i> (%)	65 (83)
Cognitive impairment, <i>n</i> (%)	
Severe	16 (21)
Moderate	27 (35)

(Continues)

**TABLE 1** (Continued)

Characteristic	Value
Mild	26 (33)
None	2 (3)
Not reported	7 (9)

Abbreviations: ASM, antiseizure medication; Br, bromide; BRV, brivaracetam; CBD, cannabidiol; CLB, clobazam; FFA, fenfluramine; GTCS, generalized tonic-clonic seizure; LEV, levetiracetam; STP, stiripentol; TPM, topiramate; VPA, valproic acid.

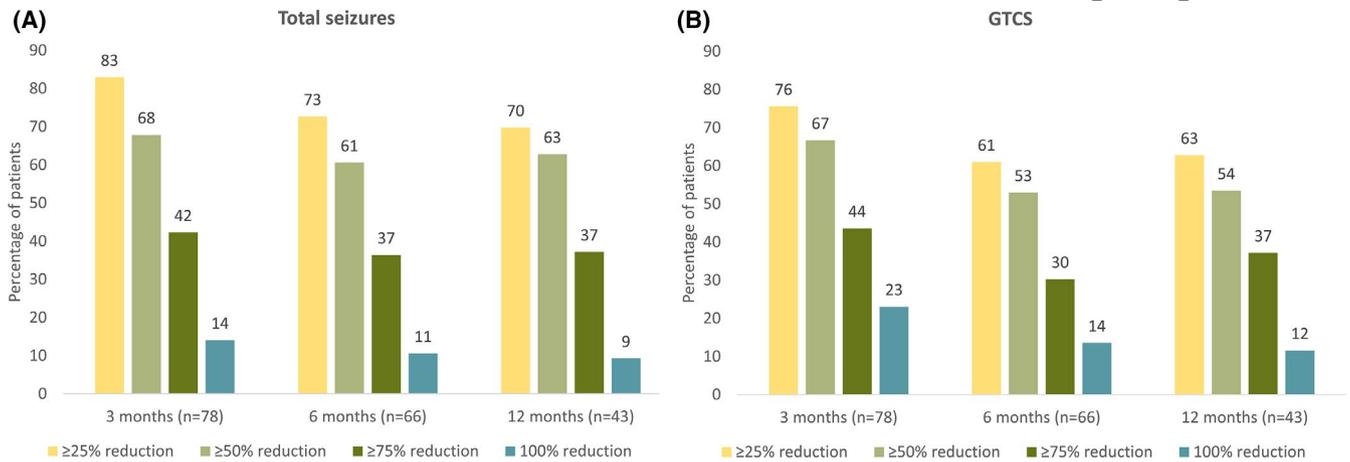
<sup>a</sup>In the 6 months prior to the start of FFA treatment.

<sup>b</sup>Average over the 3 months prior to the start of FFA treatment.

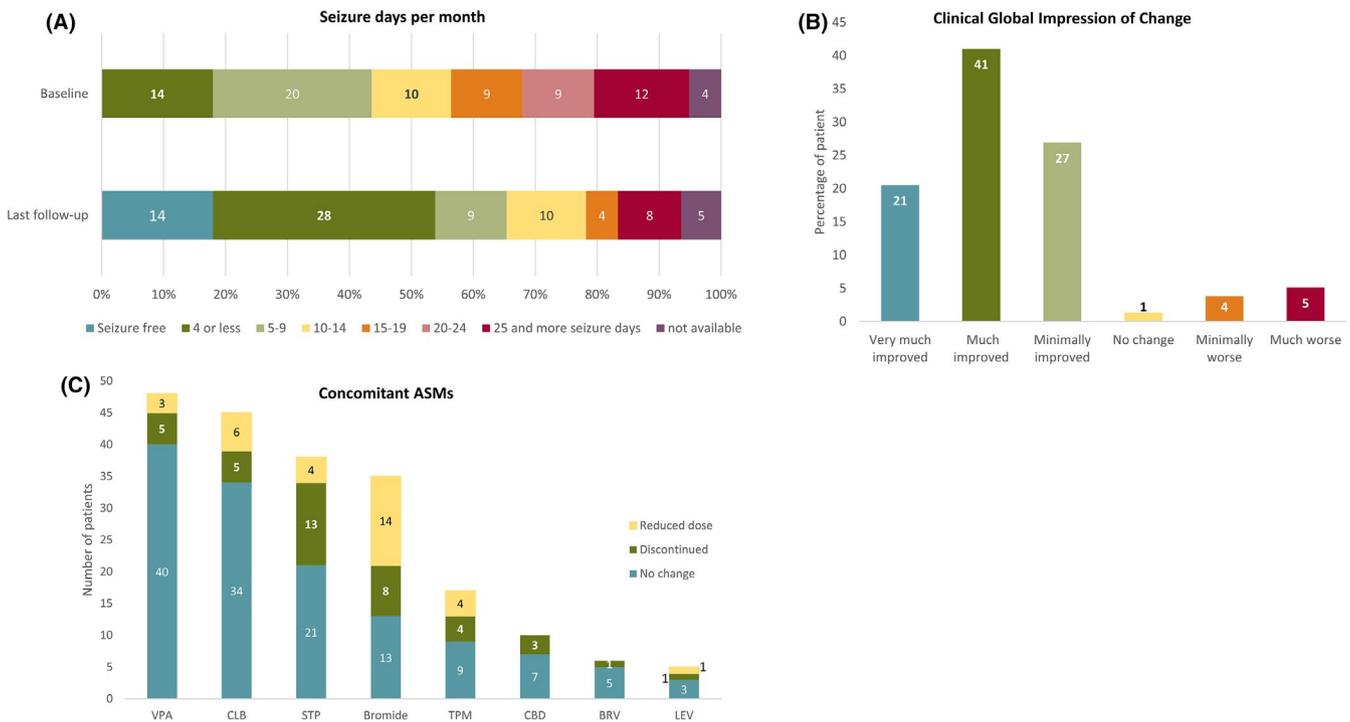
with FFA, the percentage of patients with  $\geq 25\%$ ,  $\geq 50\%$ , and  $\geq 75\%$  reductions in total seizures compared to baseline was 83% ( $n = 65$ ), 68% ( $n = 53$ ), and 42% ( $n = 33$ ), respectively. Eleven (14%) patients were free of seizures, and a further 12 (15%) patients had only one day of seizures per month. For GTCSs, the percentage of patients with  $\geq 25\%$ ,  $\geq 50\%$ , and  $\geq 75\%$  reductions was 76% ( $n = 59$ ), 67% ( $n = 52$ ), and 44% ( $n = 34$ ), respectively, at 3 months, with 18 (23%) patients being free of GTCSs; data were missing (i.e., GTCS frequency was not accurately recorded) for six patients, and in two patients no GTCSs were reported at baseline. Response rates for total seizures and GTCS were similar at 6 months and 12 months, although the numbers of patients with follow-up at these time points was lower; at 6 months, there were 66 patients who had follow-up data, and data were not available for an additional nine patients for all seizures (data were missing for seven patients, and two had discontinued FFA before the 6-month follow-up period was complete); at 12 months, there were 43 patients who had follow-up data, and data were not available for an additional nine patients for all seizures (one patient with missing data and eight who discontinued). Details are presented in Table S2.

### 3.3.2 | Seizure days

Figure 2A shows the percentage of patients according to their seizure days per month at baseline and at last follow-up across seven incremental categories from being seizure-free to having  $\geq 25$  seizure days per month. Increases in the percentage of patients who were seizure-free or with  $< 4$  seizures per month were observed at last follow-up compared to baseline, with respective decreases across the categories of those who had  $\geq 5$  seizure days per month. During FFA treatment, the median seizure days per month decreased from 10.0 (range = .5–30, mean [SD] = 12.9 [9.2] days/month) in the 3 months before FFA initiation to 3.0 (range = 0–30, mean [SD] = 7.1 [9.1] days/month) in the last 3-month period of FFA treatment ( $p < .001$ ).



**FIGURE 1** Responder rates over time for (A) total seizures and (B) generalized tonic-clonic seizures (GTCS). At 3 months, data were missing (i.e., seizure frequency was not accurately recorded) for 0 patients for all seizures and six patients for GTCS, and in two patients no GTCS were reported at baseline; at 6 months there were 66 patients who had follow-up data, and at 12 months there were 43 patients who had follow-up data; for details please refer to Table S2



**FIGURE 2** (A) Percentage of patients according to seizure days per month across seven incremental categories at baseline and at the last follow-up after initiation of fenfluramine (FFA). (B) Physician-assessed Clinical Global Impression of Change. (C) Number of patients with concomitant antiseizure medications (ASMs) at baseline (represented as the entire stacked column), and no changes, discontinuations, and dose reductions during FFA treatment. BRV, brivaracetam; CBD, cannabidiol; CLB, clobazam; LEV, levetiracetam; STP, stiripentol; TPM, topiramate; VPA, valproic acid

### 3.3.3 | Status epilepticus

In the 6 months prior to the start of FFA treatment, 22 (28%) patients experienced at least one episode of SE (Table 1). While being treated with FFA (median treatment duration

= 255.5 days), significantly fewer patients reported at least one episode of SE ( $n = 11$  [14%],  $p = .005$ ). Overall, during treatment with FFA, six patients had one episode, two had two episodes, and three had an unknown number of episodes over the entire treatment period.

### 3.3.4 | Clinical Global Impression of Change

Using the CGIC scale, physicians rated the patients treated with FFA as very much improved for 16 (21%) patients, much improved for 32 (41%) patients, and minimally improved for 21 (27%) patients (Figure 2B). In addition, one (1%) patient was rated as unchanged, three (4%) as minimally worse, and four (5%) as much worse (Figure 2B).

### 3.4 | Impact of FFA on concomitant ASM consumption

After starting treatment with FFA, 35 (45%) patients discontinued at least one concomitant ASM, and the dose of a concomitant ASM was reduced in a further 18 (23%) patients. In 20 (26%) patients there was no change of the concomitant ASM, whereas in three (4%) patients concomitant ASMs were increased in dose and in two (3%) patients further new ASMs were introduced. ASMs that were discontinued included STP ( $n = 13$ ), bromide ( $n = 8$ ), VPA ( $n = 5$ ), CLB ( $n = 5$ ), TPM ( $n = 4$ ), and CBD ( $n = 3$ ), and doses were reduced for bromide ( $n = 14$ ), CLB ( $n = 6$ ), STP ( $n = 4$ ), TPM ( $n = 4$ ), and VPA ( $n = 3$ ; Figure 2C).

### 3.5 | Retention time

The retention time, assessed using Kaplan–Meier survival curves for all patients and according to adults ( $n = 13$ , 17%) and children ( $n = 65$ , 83%), is shown in Figure 3.

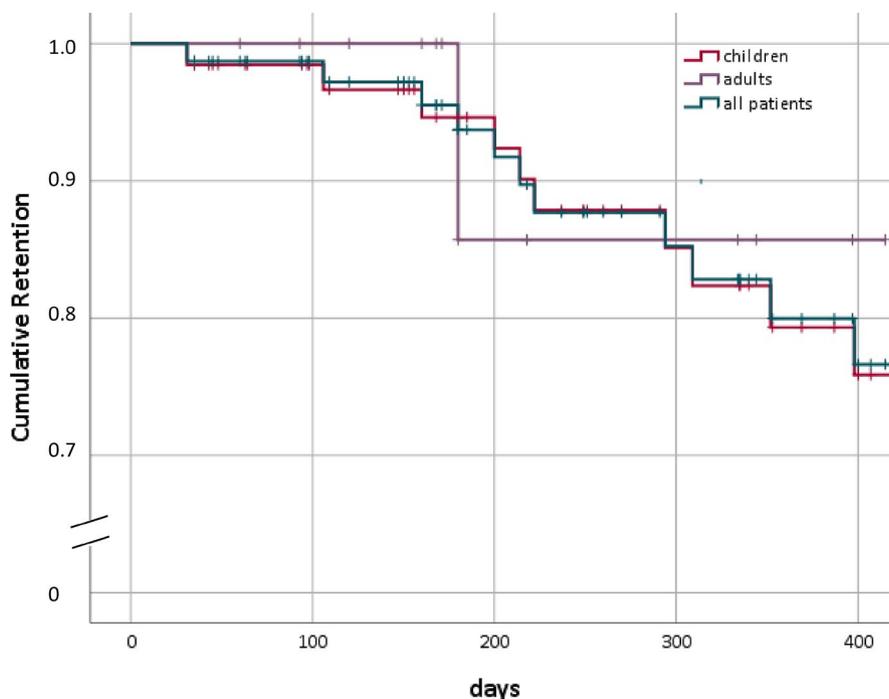
For all patients, the median retention time was 255.5 days. There was no difference in the retention rate in adults (92%) and children (83%; log-rank test  $p = .789$ ) during the observational period.

### 3.6 | Adverse events

Overall, AEs were reported in 44 (56.4%) patients treated with FFA. The most common AEs were somnolence ( $n = 28$ , 36%), decreased appetite ( $n = 17$ , 22%), and ataxia ( $n = 6$ , 8%; Table 2). One patient discontinued FFA due to somnolence, one due to decreased appetite, and two due to psychobehavioral AEs. Echocardiographic examinations revealed no signs of cardiac valvulopathy, valvular heart disease, or pulmonary hypertension. We did not observe any deaths during the study treatment period.

## 4 | DISCUSSION

Under the CUP in Germany, FFA demonstrated efficacy across a range of outcomes in a large cohort of patients; this is the largest real-world study in terms of patient numbers treated with FFA in DS patients to date. DS is difficult to treat, and the patients in this study, including both children and adults, were drug-resistant and had a high symptom burden including frequent seizures and episodes of SE, with 55% having moderate or severe cognitive impairment.



**FIGURE 3** Retention of fenfluramine in the complete cohort and in adults and children. The y-axis (cumulative retention) starts at .7.

**TABLE 2** Adverse events ( $n = 78$ )

Adverse event	n (%)
Somnolence	28 (36)
Decreased appetite	17 (22)
Ataxia	6 (8)
Increase in behavioral problems	5 (6)
Aggressive behavior	3 (4)
Gastrointestinal	2 (3)
Edema	1 (1)

At a mean dose of FFA of .40 mg/kg/day, FFA was associated with  $\geq 50\%$  seizure responder rates for total seizures of 68%, 61%, and 63% at 3, 6, and 12 months, respectively, and for GTCSs of 67%, 53%, and 54%, respectively. In the pivotal RCTs,  $\geq 50\%$  responder rates for convulsive seizures of 38%–68% across different doses/regimens were reported,<sup>6,7</sup> with rates of 64.5% observed in the OLE extension (median duration of treatment = 631 days; Table S3).<sup>8–10</sup> Specchio et al.,<sup>16</sup> reporting on the Italian EAP experience, demonstrated a  $\geq 50\%$  responder rate for convulsive seizures of 71.1%, higher than in our study and in the RCTs. Although it is not surprising that there are some differences in the responder rates between studies, possibly due to differences in patient characteristics, prior and concomitant treatments, doses, and follow-up times, these real-world studies and RCTs have consistently demonstrated that FFA results in a reduction in seizures in a substantial proportion of patients with DS. Furthermore, the ultimate treatment goal of seizure freedom or near freedom from seizures has been observed in a notable proportion of patients in our study (29.5% with  $\leq 1$  seizure per month) and others,<sup>6,7,16</sup> with Nabbout et al.<sup>7</sup> reporting a statistically significant difference in the proportion of patients having  $\leq 1$  convulsive seizure during the 14-week treatment period with FFA compared to placebo (Table S3). Of note, FFA has also shown efficacy in reducing seizures in other drug-resistant epilepsy syndromes including Lennox–Gastaut syndrome and CDKL5 deficiency disorder.<sup>21,22</sup>

As well as reductions in total seizures and GTCSs, we found a statistically significant reduction in seizure days, in line with data from the pivotal RCTs that have reported increases in seizure-free days and statistically significant increases in seizure-free intervals.<sup>6,7</sup> In addition, FFA was associated with improvements in overall condition (physician-rated CGIC). This is in agreement with other studies, including the pivotal RCTs,<sup>6–8</sup> and recent data from the FFA EAP in the United States (Table S3).<sup>23</sup> Furthermore, we also observed reductions in episodes of SE, a very serious manifestation of DS, associated with hospitalizations, long-term neurological and cognitive sequelae, and even death, as well as a high health care burden.<sup>2,24</sup> It is also notable that during treatment with FFA

in our study, 45% of patients were able to discontinue concomitant ASMs, and the dose was tapered in a further 23% of patients. Specchio et al.<sup>16</sup> also reported reductions in the medication burden (discontinuations or dose reductions of concomitant ASMs) with FFA in 46% of patients, although the proportion of patients who discontinued an ASM was lower than in our study (14% vs. 45%). This may be due to the longer follow-up in our study, allowing more time to assess whether the patient had achieved a sustained period of seizure control before discontinuing concomitant ASMs.

FFA had a good retention rate over a sustained period, further providing evidence of its effectiveness and good tolerability. Only eight (10.3%) patients discontinued due to lack of efficacy. The retention time of FFA did not differ between adults and children, suggesting that FFA is efficacious and tolerable across all age groups, although it should be noted that the subgroup of adults was quite small ( $n = 13$ ). The tailoring of medications in individual patients to the lowest doses and number of drug combinations to control AEs and reduce the pill burden may also have contributed to the good retention rate.

FFA was generally well tolerated, with only four patients discontinuing treatment due to an AE. Decreased appetite was one of the most commonly reported AEs in the pivotal RCTs (34% across the FFA trials in patients with DS).<sup>25</sup> It was also a commonly observed AE in our study and the Italian study, but in only 22% and 13% of patients, respectively; only one patient discontinued due to this AE in our study and none in the Italian study. In addition, in agreement with other studies,<sup>16,25</sup> we also commonly observed somnolence, although it only resulted in one patient discontinuing FFA. There were no cases of sudden unexpected death in epilepsy (SUDEP) and no deaths during the FFA treatment period, although evaluating the effects of FFA on SUDEP and mortality requires a study with a larger population and a longer surveillance period. In this respect, data from a post hoc analysis of a large number of patients treated with FFA ( $n = 732$ ; 1108.2 person-years of observation) suggest that FFA is associated with marked reductions in SUDEP and overall mortality.<sup>26</sup>

Importantly, none of our patients experienced clinical or echocardiographic signs of cardiac valvulopathy, valvular heart disease, or PAH, in line with the Italian experience and the OLE of the pivotal RCTs.<sup>16,27</sup> In the OLE, regular echocardiographic examinations found no cases of valvular heart disease or PAH in 232 patients (median duration of treatment = 256 days, range = 58–634). Overall, FFA at the low doses used for DS appears to have a low risk of developing these cardiovascular complications; however, in accordance with the regulatory requirements, cardiac monitoring should be performed in patients treated with FFA.<sup>28–30</sup>

This study has several advantages as well as some limitations. We analyzed a comprehensive range of efficacy

outcomes, and the population size was large in the context of a rare disease. Prior and concomitant treatments included a wide range of ASMs representative of the current treatment pathway including STP (concomitant use in 49%) and CBD (concomitant use in 13%). The patient population is also likely to be representative of other countries, although the concomitant use of bromide may be higher than in other European countries and the United States but similar to Japan.<sup>4</sup> An important limitation is the lack of a control group, although our results are in line with those reported in the pivotal RCTs.<sup>6,7</sup> In addition, a longer follow-up is required to determine the extent of sustained efficacy and safety, and further studies are required to determine the impact on cognitive and behavior impairment and quality of life (QoL). Furthermore, absences and myoclonia are very challenging to count accurately, a limitation shared with other clinical studies of DS. Finally, the CGIC was only measured by the clinicians, and not also by parents or caregivers, which would have provided an additional perspective. Furthermore, because this was an observational study where the clinicians were not blinded to the treatment, there is potential for bias in partially subjective outcomes such as the CGIC. In addition, clinicians may have recorded improvements in seizures as opposed to truly global improvements, although the clinicians were educated in the use of the CGIC. Overall, studies evaluating a range of QoL measures are required to truly assess the impact of FFA on the QoL of patients and caregivers.<sup>31</sup>

In conclusion, in a large cohort of patients, FFA demonstrated efficacy across a range of outcomes including clinically meaningful reductions in total seizures and GTCs, seizure days per month, and episodes of SE, and was well tolerated with a good retention rate, providing valuable information for real-world practice.

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## CONFLICT OF INTEREST

A.S. reports personal fees and grants from Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals, Marinus Pharma, Medtronic, UCB, and Zogenix. M.P. reports personal fees from Zogenix. T.M. reports personal fees and grants from Arvelle

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## AUTHOR CONTRIBUTIONS

All authors were involved in the conception and design of the study, acquisition and analysis of data, and drafting of the manuscript and/or figures.

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## SUPPORTING INFORMATION

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

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