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ORIGINAL ARTICLE

Cost-effectiveness of fenfluramine as add-on treatment in the management of Dravet Syndrome: A real-world multicenter study

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Abstract

Objective: Dravet syndrome (DS) is a rare disease with a high clinical and socioeconomic impact on patients, society, and the healthcare system. The recent approval of therapies such as fenfluramine (FFA) has transformed the treatment landscape; however, data on their cost-effectiveness are still scarce. This study evaluates the real-world cost-effectiveness of adding FFA to existing therapies for DS patients from the Italian National Healthcare System perspective.

Methods: This retrospective multicenter observational study included 124 Italian DS patients initiating FFA as add-on treatment between February 2017 and August 2022 and followed until December 2022 or disenrollment (post-FFA period). Data on drug treatments, healthcare resource utilization, and main outcomes—rescue medication, hospital admission, and status epilepticus (SE) episodes—were collected both in the post-FFA period and in a pre-FFA period matching each patient's follow-up duration (median 2.9 years). Annual per-patient rates and costs, with 95% confidence intervals (CI), were determined for each outcome in both periods. Incremental cost-effectiveness ratios (ICERs) with 95% CIs and cost-effectiveness acceptability curves (CEACs) were also calculated.

Results: The median age at FFA initiation was 8.5 years. Mean annual healthcare cost of patients with DS was €5740 (95% CI 2896–9930) in the pre-FFA period. FFA introduction added an annual per-patient drug acquisition cost of €16 476, but it significantly reduced frequency and costs associated with hospital admissions and acute events. ICERs were €2187 per rescue medication avoided, €12 935 per hospital admission avoided, and €17 301 per SE episode avoided.

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Significance: This real-world study demonstrates that despite increased drug acquisition costs, FFA provides clinical and economic benefits by reducing acute events and related healthcare costs. The investment required to reduce acute events is justifiable given the young age of DS patients and its impact on the healthcare system, families, and caregivers. Future research should incorporate indirect costs and a broader societal perspective.

Plain Language Summary: Dravet syndrome is a severe and rare type of epilepsy that can be very hard on patients and their families. It also puts a great burden on healthcare systems. A new treatment, fenfluramine (FFA), helps better control seizures. Although FFA increases drug treatment costs, this cost is actually balanced out by reduced emergency visits and hospital stays for severe seizures, leading to overall lower healthcare expenses.

KEYWORDS
anti-seizure, cost-effectiveness, Dravet syndrome, FFA

1 | INTRODUCTION

Dravet syndrome (DS) is a severe, lifelong developmental and epileptic encephalopathy (DEE) that begins in infancy and progresses with increasing health problems, significantly impacting both individuals and their families.[1] DS is a rare disease, determined to occur in 1:15 500 live births, and it is also the most frequent form of genetic DEE.[2,3]

People living with DS experience a high seizure burden in the first 3 years of life, with seizure types evolving over time.[1,4] Additional DS manifestations include neurodevelopmental stagnation or decline, behavioral and sleep difficulties, and motor impairment, which worsen and become more detectable throughout childhood.[1] Individuals with DS have an increased risk of general mortality in early childhood.[5]

The management and care of DS patients has a high socioeconomic impact on the family and the healthcare system. Recent studies report that caring for a child with DS is associated with significant humanistic burden and direct costs.[6–9] A recent study reported a mean direct health care cost of €6666 per patient—3 months, with the highest direct cost associated with inpatient care (28%). Indirect costs associated with caregiver were €4790 over 3 months, representing 42% of the overall cost.[9] Further, this study highlighted the significant association between seizure frequency, episodes of status epilepticus (SE), and total direct healthcare costs.

The approval of therapies such as fenfluramine (FFA), cannabidiol, and stiripentol, which have demonstrated efficacy in reducing the seizure burden in DS, has changed the treatment landscape.[1] The efficacy of this treatment should be reflected in the reduction of cost associated with the management of the clinical manifestations experienced by DS patients.

Key points

- Dravet syndrome is a severe, rare disease with a high socioeconomic impact on families, society, and healthcare systems.
- The approval of therapies such as fenfluramine (FFA) has changed the treatment landscape and requires cost-effectiveness evaluation.
- The use of FFA as an add-on treatment increased drug acquisition costs, but reduced acute events and related healthcare resource use.
- These results can help healthcare decision-makers in assessing the value of FFA and optimizing resource allocation within the Italian NHS.

A single study has assessed the costs and effectiveness associated with FFA as an add-on to standard of care (SoC) for reducing seizure frequency in DS. This study, conducted within the Swedish healthcare system, reported a lifetime cost of FFA + SoC of ~3 million SEK per patient compared with ~1.5 million SEK for SoC only, with FFA + SoC generating 15% more quality-adjusted life years (QALYs) than SoC only (21.2 vs. 18.5 over a lifetime). The differences in costs and effectiveness resulted in an incremental cost-effectiveness ratio (ICER) of ~540 000 SEK

that was below the willingness-to-pay (WTP) threshold of 1 000 000 SEK used in Sweden to define a given treatment for rare disease as cost-effective.[10] However, the Swedish study was based on a simulation model developed in Microsoft Excel® and no economic evaluations, based on real-world data, on FFA in DS patients are available in the literature.

We carried out a longitudinal real-world study with the aim of providing a cost-effectiveness analysis on the introduction of FFA as an add-on treatment in patients with DS in actual clinical practice from the Italian national healthcare system perspective.

2 | METHODS

2.1 | Study design

This is a retrospective multicenter observational study on a cohort of 124 patients with DS observed in nine Italian clinical centers, starting therapy with FFA as an add-on treatment at any age between February 2017 and August 2022. Details on inclusion and exclusion criteria for patients are reported in a previous study based on this dataset.[11]

The study collected data on clinical, demographic, and auxological (height, weight) characteristics of patients at FFA therapy initiation. Patients were followed from the start of FFA therapy until September 2022 or until disenrollment (defined as FFA therapy interruption, death, or emigration). FFA treatment, concomitant anti-seizure medications (ASMs) use and dosage, aggregated data on rescue medication administrations, hospital admissions, SE episodes were collected during the observation period, and auxological data were collected at the end of follow-up for each patient. Data on drug treatments and healthcare resource access were also recorded in a pre-FFA observation period as long as each patient's follow-up period (post-FFA observation period). All data were extracted from clinical notes, diaries, and the Residras registry, a national registry including longitudinal data of DS patients and cross-verified from patients' records.[11]

Ethical approval for data collection and analysis was obtained from local Ethics Committees of each participating institution; data were anonymized for analysis and merged into a single dataset.

2.2 | Outcomes

The main outcomes analyzed were the number of rescue medication administrations, the number of hospital admissions for SE or other acute events, and the number of SE episodes. An SE episode was defined as a seizure with a duration of 30 min or longer or a series of seizures in which the patient did not regain normal mental status between consecutive seizures.[12] SE episodes could require hospital admission or emergency department (ED) access in most cases or be treated with rescue medication out of the hospital.

2.3 | Healthcare resource use and associated cost

Healthcare resources included in the analysis were ED accesses or hospital admissions for SE episodes or hospital admissions for other acute events and drug therapies: FFA and other ASMs (acetazolamide, sodium valproate, potassium bromide, cannabidiol, clobazam, clonazepam, ethosuximide, felbamate, phenobarbital, hydrocortisone, levetiracetam, lorazepam, nitrazepam, perampanel, risperidone, stiripentol, topiramate, zonisamide) and rescue medications (midazolam and diazepam).

We multiply the quantity of resources by their unit costs to estimate the costs associated with healthcare resource consumption (Table 1). Hospital admission unit cost was computed as the average cost of Diagnosed Related Groups (DRGs) associated with hospital admissions registered annually in the patients treated at the Neuroscience and Medical Genetics Department of Meyer Children's University Hospital—IRCCS. The cost of patients hospitalized due to SE also included expenses for intensive care unit[13] and ED access[14] when applicable. ED cost was associated with SE episodes that did not require hospital admission.

The regional technical administrative support organization for Tuscany (ESTAR) tender award prices[15] were used for pharmacological therapies and multiplied by the indicated dosage. The cost associated with rescue therapies was defined by the average cost of the therapies used for managing seizures: midazolam and diazepam.

2.4 | Statistical analysis

Main patients' characteristics at FFA starting and during the post-FFA observation period are reported as median (q1–q3) for continuous data and relative frequencies for categorical variables. Main outcomes, healthcare resource use, and related costs were computed in the pre- and post-FFA observation periods; and reported as annual per-patient numbers or costs with 95% confidence intervals (CI). ASMs use was reported as daily numbers per patient. The study compared all measures between pre-FFA and post-FFA observation periods, calculating differences (Δ)

TABLE 1 Costs of healthcare resources.

Parameter	Cost (€)	Measure unit	Source
Fenfluramine	3.1213	€/mg	ESTAR tender[15]
Other therapies			
Acetazolamide	0.0006	€/mg	ESTAR tender
Valproate	0.0004	€/mg	ESTAR tender
Potassium bromide	-	-	-
Cannabidiol	0.0589	€/mg	Estimated as an average discount between the factory price and the ESTAR tender
Clobazam	0.0155	€/mg	ESTAR tender
Clonazepam	0.0326	€/mg	ESTAR tender
Ethosuximide	0.0005	€/mg	Estimated as an average discount between the factory price and the ESTAR tender
Felbamate	0.0010	€/mg	Estimated as an average discount between the factory price and the ESTAR tender
Phenobarbital	0.0004	€/mg	ESTAR tender
Hydrocortisone	0.4457	€/mg	ESTAR tender
Levetiracetam	0.0004	€/mg	ESTAR tender
Lorazepam	0.0000	€/mg	ESTAR tender
Nitrazepam	0.0327	€/mg	ESTAR tender
Perampanel	0.6026	€/mg	ESTAR tender
Risperidone	0.0098	€/mg	ESTAR tender
Stiripentol	-	-	-
Topiramate	0.0081	€/mg	ESTAR tender
Zonisamide	0.0031	€/mg	ESTAR tender
Other healthcare resources			
Rescue medications[a]	0.9723	€	ESTAR tender
Hospital admission for SE[b]	4792.51	€	Average cost of patients related DRGs; Belisari et al.[13]—Progetto Mattoni[14]; Rivaluta.istat.it[d]
Other hospital admissions[c]	2504.84	€	

Abbreviations: DRG, diagnosis-related group; SE, status epilepticus.

[a]Mean cost of available rescue medications—midazolam and diazepam.

[b]Mean cost of DRGs related to the disease (€2170.74) with a discounted correction factor for the use of intensive unit (€2.053867) plus a discounted cost of emergency access (€334.10).

[c]Mean cost of DRGs related to the disease (€2170.74) plus a discounted cost of emergency access (€334.10).

[d]https://rivaluta.istat.it/.

in annual per-patient numbers and costs with 95% CI. The number of concomitant therapies per patient and the frequency of use of each ASM in the pre- and post-FFA observation periods were compared using Bowker's Symmetry and McNemar tests, respectively.

Finally, incremental cost-effectiveness ratio (ICER) with 95% CI was computed for the main outcomes analyzed, specifically the average cost-per-event avoided, such as rescue medication, hospital admission, and SE episode. CI was computed as the 2.5th and 97.5th percentiles of each variable distribution obtained from 1000 bootstrap simulations. Cost-effectiveness acceptability curve (CEAC) for each outcome was also analyzed using 1000 bootstrap simulations and varying WTP thresholds ranging from €0 to €100 000. The CEAC illustrates the probability of being cost-effective at different WTP thresholds, which is the amount of money a customer is prepared to pay to obtain a particular good or service.[16]

TABLE 2 Patients' main characteristics.

Main characteristics	Value
N	124
Female, *n* (%)	65 (51%)
Age at diagnosis (years), median (q_1–q_3)	1.0 (1.0–3.0)
Age at FFA treatment starting (years), median (q_1–q_3)	8.5 (5.0–14.5)
Age classes at FFA treatment, *n* (%)	
≤6 years	51 (41%)
7–11 years	27 (22%)
≥12 years	46 (37%)
Follow-up times[a] (years), median (q_1–q_3)	2.9 (2.0–3.4)
Weight at FFA treatment starting (kg), median (q_1–q_3)	29.0 (19.0–52.5)
Weight at follow-up end (kg), median (q_1–q_3)	34.0 (22.0–59.9)
Δ Weight (kg), median (q1–q3)	3.0 (0.0–6.0)
FFA dosage at treatment starting (mg/kg/day), median (q_1–q_3)	0.2 (0.2–0.4)
FFA dosage at follow-up end (mg/kg/day), median (q_1–q_3)	0.5 (0.35–0.65)

Abbreviations: FFA, fenfluramine; q1, first quartile; q3, third quartile.

[a]Observation time in the pre- and post-FFA observation periods.

3 | RESULTS

The study included 124 patients with a clinical diagnosis of DS, 51% of whom were female (Table 2). The median age at clinical diagnosis was 1.0 year, and the median age at the start of FFA therapy was 8.5 years (q_1–q_3 5.0–14.5). At FFA initiation, 41% of patients were 6 years old or younger, and 37% were aged 12 years or older; this group included 13 patients aged 14–17 and 23 adults, with the oldest patient being 38 years old. The median follow-up time was 2.9 years.

The initial mean dosage of FFA was 0.2 mg/kg/day, increasing to 0.5 mg/kg/day at the end of the post-FFA period. During this period, patients showed a median weight increase of 13% (q_1–q_3 0%–25%).

3.1 | Outcomes and healthcare resource use

In the pre-FFA observation period (median duration 2.9 years, q_1–q_3 2.0–3.4), patients annually required an average of 8.6 rescue medications, 1.5 hospital admissions, and had 1.2 SE episodes (Table 3). In the post-FFA

TABLE 3 Cost-effectiveness analysis.

	Pre-FFA observation period	Post-FFA observation period	Δ (Post − Pre)
Annual per-patient number			
Concomitant ASMs (daily number)	2.7 (2.6; 2.9)	2.4 (2.3; 2.6)	−0.3 (−0.4; −0.2)
Rescue medications	8.6 (5.5; 12.1)	2.6 (1.4; 4.2)	−6 (−8.5; −3.7)
Hospital admissions	1.5 (0.7; 2.7)	0.5 (0.3; 0.6)	−1 (−2.2; −0.3)
SE episodes	1.2 (0.5; 2.1)	0.4 (0.1; 1)	−0.8 (−1.3; −0.4)
Annual per-patient cost (€)			
Concomitant ASMs	528 (264.9; 1046.6)	779.3 (399.1; 1247.3)	251.3 (−149.7; 695.6)
FFA	-	16 475.7 (14 964.5; 18 049.7)	16 475.7 (14 964.5; 18 049.7)
Rescue medications	8.3 (5.3; 11.7)	2.5 (1.4; 4.1)	−5.8 (−8.3; −3.6)
Hospital admissions	5009.9 (2264.0; 9109.4)	1409.7 (938.4; 2047.7)	−3600.2 (−7457.6; −1158.7)
ED access	193.5 (34.0; 469.0)	99.4 (0.0; 285.2)	−94.2 (−30.1; −180.3)
Total	5739.8 (2895.6; 9917.8)	18 766.5 (17 165.4; 20 349.2)	13 026.7 (8765.0; 16 364.7)
ICER (€/event)[a]			
Rescue medication	2187.2 (1137.9; 3997.2)		
Hospital admission	12 935.1 (4198.7; 50 333.7)		
SE episode	17 301.4 (7020.2; 44 895.3)		

Note: Resource use and outcomes in the pre- and post-FFA treatment starting observation periods. Values are reported as mean (95% CI).

Abbreviations: ED, emergency department; FFA, fenfluramine; SE, status epilepticus.

[a]ICER = Δ costs/−Δ events: Δ = post – pre-FFA values. Δ = difference.

observation period, the number of events was reduced for each outcome analyzed, with a statistically significant annual mean reduction of 6.0 rescue medication uses, 1.0 hospital admission, and 0.8 SE episodes per patient.

The average number of daily concomitant ASMs also decreased, from 2.7 to 2.4 per patient (Table 3). Detailed distribution of per-patient number of ASMs use is reported in Figure S1, showing an increase in the percentage of patients using two or fewer ASMs, from 30% in the pre-FFA period to 47% in the post-FFA period. The most commonly used ASMs in both periods were valproate, clobazam, stiripentol, topiramate, clonazepam (Table S1). The use of stiripentol had a statistically significant decrease in the post-FFA period.

3.2 | Healthcare costs

The per-patient annual healthcare cost in the pre-FFA period was €5740 (95% CI: 2896–9930) (Table 3). The main driver of total cost was hospital admission, with an annual per-patient cost of €5009, followed by costs for ED visits for SE episodes, ASM therapy, and rescue medications. In the post-FFA period, the mean annual healthcare cost rose to €18 767 (95% CI: 17 165–20 349). The introduction of FFA added €16 476 per patient annually, making it the largest contributor to total costs, followed by hospital admissions, ED visits, ASMs, and rescue medications. While the cost of concomitant ASMs remained stable, all other healthcare-related costs had a statistically significant decrease.

3.3 | Cost-effectiveness analysis

The cost-effectiveness analysis showed an average cost of €2187 per patient to avoid one rescue medication use, €12 935 to avoid one hospital admission, and €17 301 to avoid one SE episode (Table 3). The introduction of FFA as add-on therapy was cost-effective for all three outcomes analyzed (Figure 1). The probability of cost-effectiveness at different WTP values is reported in Figure 2. FFA therapy was 100% cost-effective for avoiding rescue medication use at WTP thresholds of €5000 or more. The probability of cost-effectiveness reached or exceeded 80% at WTP thresholds of €30 500 for hospital admission and €25 500 for SE episodes.

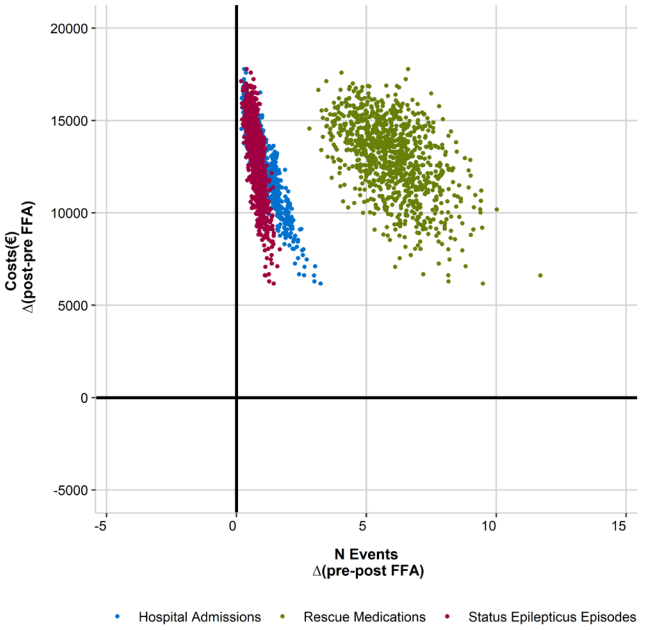

FIGURE 1 Cost-effectiveness plane for the main outcomes analyzed. Δ, difference; FFA, fenfluramine.

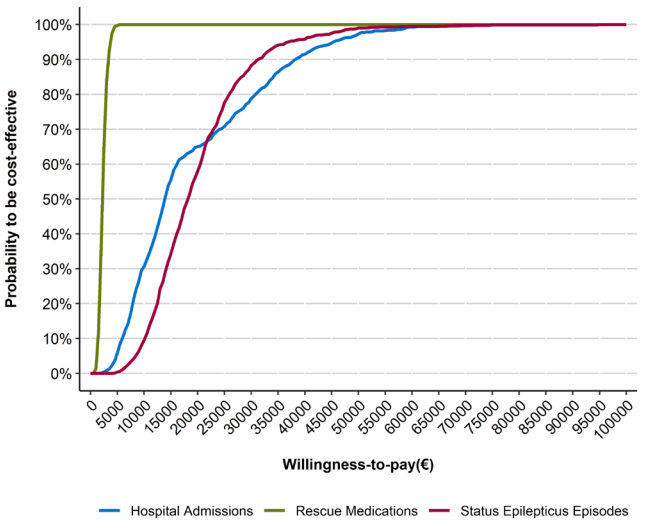

FIGURE 2 Cost-effectiveness acceptability curve for the main outcomes analyzed.

4 | DISCUSSION

We assessed the costs and effectiveness associated with FFA as an add-on to SoC for reducing seizure frequency in patients with DS, using real-world data from nine Italian clinical centers specialized in the management of DS. The introduction of FFA as an add-on treatment resulted in an additional annual per-patient cost of €16 476 while significantly reducing the number and cost of all key clinical outcomes analyzed: rescue medications, hospital admissions, and SE episodes. The ICERs indicated the additional costs associated with FFA to avoid one unit of each outcome. Based on this analysis, the additional cost to avoid one rescue medication use was €2187 per patient, €12 935 to avoid one hospital admission, and €17 301 to avoid one SE

episode. All ICERs are below the threshold of €33 000 per QALY or outcome gained, which represents a key benchmark identified by Russo and colleagues for the Italian setting,[17] although the accepted WTP thresholds for rare diseases could be higher. These results suggest that FFA represents a reasonable investment when considering the improved outcomes and reduced burden of seizures, hospital admissions, and SE episodes in the Italian context. Moreover, our findings are in line or even more favorable than those reported for treatments in other rare pediatric conditions, such as hemophilia.[18–20] For instance, different cost-effectiveness studies on recombinant Factor VIII (FVIII) prophylaxis in hemophilia have used the number of bleeding episodes avoided as an outcome, producing ICERs between €6000 and €23 000 per bleeding avoided. These values have been deemed acceptable by many healthcare systems and have supported the reimbursement of FVIII prophylaxis in several countries, including Italy.[18–20] One example is the ESPRIT study, a randomized controlled clinical trial that compared the efficacy of prophylaxis and episodic therapy in preventing hemarthroses and image-proven joint damage in children (age 1–7 years) with severe hemophilia A (factor VIII <1%). This study reported a yearly prophylaxis cost of €79 668 compared with €35 829 of episodic therapy, with an ICER of €7537 per bleeding event avoided,[18] a figure falling between the ICERs we found for FFA. Considering these comparisons, the investment in FFA appears reasonable not only from a clinical and healthcare system perspective but even more from the perspective of families, caregivers, and society. As previously reported, indirect costs related to caregiver and society burden account for 42% of the overall cost of DS, and both direct and indirect costs are significantly associated with seizure frequency and SE episodes. Reducing these events can therefore result in broader societal savings.[9]

The medical and social costs of prolonged seizures and SE episodes, such as hospital admissions, intensive care use, and long-term consequences, are substantially higher than for shorter seizures.[21,22] For example, a German study found that while SE represented just 4% of the seizure-associated hospital admissions in patients aged 0–18 years, it accounted for 22% of the overall costs[22] In addition, reducing SE episodes also lowers the risk of severe complications, including permanent brain damage, to which patients with DS are particularly vulnerable[23]

A favorable cost-effectiveness profile has also been suggested in the literature,[24] although only one full economic evaluation is currently available.[10] The model-based simulation by Malmberg et al. showed a favorable cost-effectiveness profile for FFA + SoC in the Swedish setting, with an ICER of ~540 000 SEK per QALY gained for FFA + SoC compared with SoC alone in Sweden. This ICER is below the WTP threshold of 1 000 000 SEK used in Sweden to define a treatment for rare disease cost-effective.[10] However, these results are based on simulations that need confirmation in real-world settings. Our study provides a first attempt to fill this gap, providing first indication of the value of FFA in clinical practice.

In both model-based simulations and real-world analyses, FFA increased treatment costs associated with FFA are at least partially offset by reduced costs for managing acute events (e.g., rescue medication use, ED visits, and hospital admissions), with a significant improvement in clinical outcomes.

The increased cost of FFA could be further justified by the potential reduction in indirect costs, such as the loss of productivity experienced by parents and caregivers. Fewer seizures and SEs may reduce the time and effort required for patient care, improving the quality of life and productivity of caregivers. The present study did not collect data on these indirect costs, and our results are limited to an NHS perspective, so the ICERs reported can be considered conservative estimates. Our study presents other limitations to be considered. First, the observation period varied across patients, which may introduce variability in the results. Second, consistent with the pre/post study design, we acknowledge the potential influence of non-FFA treatment factors on cost-effectiveness analysis. Specifically, following the introduction of FFA as an add-on treatment, the use of other ASMs in clinical practice has been reduced (e.g., stiripentol). This contributes to a minor reduction in costs in the post-period, but does not seem to significantly alter the primary conclusions regarding cost-effectiveness driven by the reduction in seizure events. Thirdly, the study collected aggregated data on the use of resources; consequently, limiting the precision of our cost-per-event estimates. Additionally, we did not include the costs of routine echocardiographic monitoring (every 6 months), which is mandatory during FFA treatment. This omission introduced an additional, though negligible, underestimation of costs.

In conclusion, we assessed the real-world cost-effectiveness of FFA as an add-on to Soc in DS patients. While FFA increases drug acquisition costs, this is partly offset by reduced costs associated with acute events and disease management. ICERs of €2187 per rescue medication avoided and €12 935 per hospital admission avoided suggest a reasonable investment considering the early onset age of DS and its significant impact on families and caregivers. Our results can help healthcare decision-makers in understanding the value of FFA and optimizing the use of healthcare resources within the Italian NHS. Future studies should include the indirect costs and social perspective to offer a more comprehensive assessment of the value associated with FFA treatment. Moreover, due to variations in

pricing, reimbursement policies, and clinical practice, the direct generalizability of these findings to other healthcare systems outside Italy should be interpreted with caution.

AUTHOR CONTRIBUTIONS

All authors satisfy the ICMJE guidance by substantially contributing to the design, analysis, and interpretation of the work, drafting of the manuscript, final approval of the manuscript, and all agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

P.A.C. has received grants and personal fees from Roche, Almirall, Otsuka, Novartis, Daiichi Sankyo, and Bayer. Takeda. A.B. has received speaker honoraria from UCB. S.B. has served as a consultant or received honoraria for lectures and consulting activities from Angelini Pharma, Biocodex, Eisai, Jazz Pharmaceutics, Longboard Pharmaceutics, Lusofarmaco. N.S. has served on scientific advisory boards for GW Pharma, BioMarin, Arvelle, Marinus, and Takeda; has received speaker honoraria from Eisai, BioMarin, Livanova, Sanofi; has served as an investigator for Zogenix, Marinus, BioMarin, UCB, Roche. V.D. has served as an investigator for Biocodex. M.T. has served as a consultant or received honoraria for lectures and consulting activities from Biocodex and BioMarin Pharmaceutical. A.C. received speaker's honoraria from UCB. L.G.M. has received grants and personal/speaker fees from Bayer AG, Boehringer Ingelheim, Pfizer, GSK, and Roche. R.G. has served as a consultant or received honoraria for lectures and consulting activities from Angelini Pharma, Novartis, Biocodex, BioMarin, Eisai, Jazz Pharmaceutics, Ethypharm, Rapport Therapeutics, SK Life Science Inc., GRIN Therapeutics, Stoke, Takeda, UCB Pharma; and has been a Principal Investigator for clinical trials for Eisai, UCB Pharma, Zogenix, Lundbeck, Loulou Foundation, Marinus, TEVA, and Takeda. The remaining authors have no conflict of interest to declare. 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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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