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The contribution of fenfluramine to the treatment of Dravet syndrome in Spain through Multi-Criteria Decision Analysis

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ABSTRACT

Introduction: Dravet Syndrome (DS) is a severe, developmental epileptic encephalopathy (DEE) that begins in infancy and is characterized by pharmaco-resistant epilepsy and neurodevelopmental delay. Despite available antiseizure medications (ASMs), there is a need for new therapeutic options with greater efficacy in reducing seizure frequency and with adequate safety and tolerability profiles.

Fenfluramine is a new ASM for the treatment of seizures associated with DS as add-on therapy to other ASMs for patients aged 2 years and older. Fenfluramine decreases seizure frequency, prolongs periods of seizure freedom potentially helping to reduce risk of Sudden Unexpected Death in Epilepsy (SUDEP) and improves patient cognitive abilities positively impacting on patients' Quality of Life (QoL).

Reflective Multi-Criteria Decision Analysis (MCDA) methodology allows to determine what represents value in a given indication considering all relevant criteria for healthcare decision-making in a transparent and systematic manner from the perspective of relevant stakeholders. The aim of this study was to determine the relative value contribution of fenfluramine for the treatment of DS in Spain using MCDA.
Method: A literature review was performed to populate an adapted a MCDA framework for orphan-drug evaluation in Spain. A panel of ten Spanish experts, including neurologists, hospital pharmacists, patient representatives and decision-makers, scored four comparative evidence matrices. Results were analyzed and discussed in a group meeting through reflective MCDA discussion methodology.
Results: Dravet syndrome is considered a severe, rare disease with significant unmet needs. Fenfluramine is perceived to have a higher efficacy profile than all available alternatives, with a better safety profile than stiripentol and topiramate and to provide improved QoL *versus* studied alternatives. Fenfluramine results in lower other medical costs in comparison with stiripentol and clobazam. Participants perceived that fenfluramine could lead to indirect costs savings compared to available alternatives due to its efficacy in controlling seizures. Overall, fenfluramine's therapeutic impact on patients with DS is considered high and supported by high-quality evidence.

Abbreviations: A&E, accident and emergency; AEs, adverse events; AEMPS, Spanish Medicines Agency; ASM, antiseizure medication; BRIEF, Behavior Rating Inventory of Executive Function; CGI-I, clinical global impression-improvement scale; DEE, developmental epileptic encephalopathy; DS, Dravet Syndrome; EMA, European Medicines Agency; HRQoL, Healthcare-Related Quality of Life; ITC, indirect treatment comparison; LR, literature review; MCDA, Multi-Criteria Decision Analysis; MCSF, monthly convulsive seizure frequency; NHS, National Healthcare System; ObsRO, Observer-Reported Outcomes; OR, odds ratio; OLE, Open-Label Extension Study; PedsQL, Pediatric QoL scale; P&R, pricing and reimbursement; PAH, pulmonary arterial hypertension.

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Conclusions: Based on reflective MCDA, fenfluramine is considered to add greater benefit in terms of efficacy, safety and QoL when compared with available ASMs.

1. Introduction

Dravet syndrome (DS) is a severe, developmental epileptic encephalopathy (DEE) that begins in infancy, characterized by intractable seizures [1,2]. Dravet syndrome is associated with mutations in the sodium channel alpha-1 subunit gene SCN1A [3]. Seizures begin in the first year of life, some of which leading to *status epilepticus* or to Sudden Unexpected Death in Epilepsy (SUDEP). From the end of the first year of age, signs of delay in cognitive and psychomotor development appear. In many cases ataxia, disorders included within the autistic spectrum, eating disorders, and growth and sleep disorders are observed. Speech is often and severely affected [4,5]. Dravet syndrome can be associated with significant premature mortality. Death may occur at any age, but more frequently during childhood, with approximately 15–20% of patients not reaching adulthood [6,7]. Sudden Unexpected Death in Epilepsy accounts for half (53–56%) of premature mortality cases [8,9]. The estimated prevalence of diagnosed DS is 1:100,000 inhabitants, equivalent to approximately 474 patients with DS in Spain. The annual incidence has been estimated to be between 1:15,700 and 1:40,000 live births, equivalent to approximately 10–26 new patients with DS every year [10,11].

To date, there is no known cure for DS. Current treatment goal is based on reducing the number of seizures by means of antiseizure medications (ASMs), usually in combination therapy. Accepted first-line agents in Spain include clobazam [12] and valproate [13] with or without topiramate [14], although these rarely provide adequate seizure control. Stiripentol is added to valproate and clobazam when the previous line has failed to control seizures (“first-add on therapy”) [10]. Two new therapies with an indication for DS have recently been approved in Spain: cannabidiol [15,16] and fenfluramine [17–19]. Both are recommended in the most recent European treatment algorithm [20] and Spanish clinical practice guidelines [21]. According to DS experts, cannabidiol and fenfluramine will be positioned in Spain as a “second add-on” therapy to stable ASM treatment. Fenfluramine, which is not restricted as an add-on treatment to any specific ASM, can be administered with regimens including and excluding stiripentol. In the latter case, patients may be ineligible for stiripentol or stiripentol-experienced. In Europe, cannabidiol must always be administered in combination with clobazam [15,16].

Dravet syndrome is one of the most drug-resistant forms of DEE and treatment with sodium channel blocker ASMs may even worsen symptoms resulting in more difficult to control patients [22,23]. Spanish neurologists with expertise in DS have established that alternative treatment options with demonstrated efficacy in terms of reduced seizure frequency, improved seizure-free periods, improved safety and tolerability profile, and with a positive impact on Quality of Life (QoL) are needed in Spain [10]. A survey conducted across patients with DS in Europe (including Spain) established that increased seizure frequency is associated with worse QoL [24]. Dravet syndrome impacts also negatively on patient relatives’ and carers’ QoL linked to the high disease burden and the constant fear of SUDEP [25,26].

Dravet syndrome is also associated with a high economic burden, both in terms of direct costs to the National Healthcare System (NHS) and indirect costs usually borne by parents and caregivers [27]. The cost of ASMs, non-seizure-related treatments and the use of healthcare resources (mainly ambulance calls, Accident and Emergency (A&E) visits, hospitalizations, and consultations with epilepsy specialists) represent the main areas of expenditure for the NHs [24]. Although no publications are available on the indirect costs associated with DS in Spain, it is well known that DS has a negative financial impact on families [24], who face out-of-pocket payment of medicines and associated therapies (e.g. physiotherapy, speech therapy, psychological therapy), home adaptation gadgets and visits to healthcare facilities (e.g. travel, lodge and subsistence costs). Moreover, parents and caregivers must frequently give up their jobs or take time off work to care for their relatives with DS, resulting in economic burden for the whole family.

Fenfluramine is indicated for the treatment of seizures associated with DS as an add-on therapy to other ASMs for patients of 2 years of age and older [18]. The efficacy and safety of fenfluramine was demonstrated in Study 1 and Study 2, two multicenter, double-blind, randomized, placebo-controlled phase 3 trials [28,29]. The long-term efficacy of fenfluramine has also been assessed in the Open-Label Extension Study (OLE) Study 1503, demonstrating long-term durability of effect (efficacy) without development of tolerance or waning [30]. Real clinical practice experience is also available from early access programs established in several EU countries, including Spain [31,32].

Fenfluramine was granted Orphan Designation by the European Medicines Agency (EMA) in 2013 [33] (maintained after marketing authorization approval on December 18th, 2020 [33,34]) and received national approval in Spain in June 2021 [17]. The product is currently undergoing pricing and reimbursement (P&R) assessment in Spain.

Reflective Multi-Criteria Decision Analysis (MCDA) offers a methodology that allows determination of what represents value in a given indication considering all relevant criteria for healthcare decision-making in a transparent and systematic manner and from the perspective of relevant stakeholders. It does also allow the determination of the relative value contribution of a drug in comparison to other alternatives [35–37].

The aim of this study was to determine the relative value contribution of fenfluramine in the treatment of DS in Spain when compared with four other treatments: cannabidiol, clobazam, stiripentol, and topiramate, using MCDA-based methodology.

2. Methods

2.1. Study design

The study was designed following MCDA methodology good practice recommendations [38,39] using the criteria and weightings developed and validated by key experts for the evaluation of orphan drugs (ODs) in Spain [40]. Cannabidiol, clobazam, stiripentol, and topiramate were chosen as comparators.

2.2. Literature review

A literature review (LR) was conducted between November 2019 and January 2020 to identify available evidence for DS, fenfluramine and the four comparators: cannabidiol, clobazam, stiripentol, and topiramate.

Published evidence was searched using biomedical databases: MEDLINE [41], Cochrane [42], and MEDES [43]. The search included articles published in English or Spanish. It was complemented with gray literature sources such as Google Scholar, patient association websites, and documents available from official sources (e.g. EMA, Spanish Medicines Agency [AEMPS], and Spanish regional and hospital evaluations). All articles identified through the search were screened by title and abstract. Articles that did not respond to the search objective or did not meet the eligibility criteria were excluded. A full-text assessment was performed with the remainder.

2.3. Reflective MCDA tool and evidence matrix development

The ODs MCDA framework was used as a starting point for the study as it reflects and defines the most appropriate criteria to assess ODs from key decision-makers in Spain perspective [40]. As reimbursed prices for fenfluramine and cannabidiol were not available at the time of the study, the quantitative "Cost of treatment (pharmacological cost)" and the contextual "Opportunity costs and affordability" criteria were excluded from the framework. The adapted framework used in the present study is shown in Fig. 1. The information extracted from the LR was used to populate the four MCDA evidence matrices to determine the relative value contribution of fenfluramine *versus* stiripentol, cannabidiol, clobazam, and topiramate for the treatment of DS in Spain. It must be noted that at the time of the study, Real World Data (RWD) for fenfluramine were not available, so the MCDA exercise was performed only using data from Study 1 and Study 2 and the OLE Study 1503 [28–30]. Also, cannabidiol was not yet marketed in Spain and its relative positioning *versus* the other three comparators was unclear; clobazam, topiramate, and stiripentol represented the standard of care. The "Non-comparative criteria" scoring scale ranged from 0 to 5 (where 0 is the worst possible score and 5 the best). The comparative criteria (efficacy/effectiveness, safety/tolerability and patient reported outcomes [PROs] criteria) were scored on a scale ranging from −5 (i.e. fenfluramine is much worse compared with the alternative) to +5 (i.e. fenfluramine is much better than the alternative).

Contextual criteria were scored using a three-point qualitative scale: positive, neutral, or negative impact.

2.4. Expert panel design and conduct of the study

The panel composed by a multidisciplinary group of 10 Spanish experts with wide experience in DS and in drug evaluation was invited to participate in the study. The panel was composed of 3 neurologists with extensive experience in the management of patients with DS in Spain and an active participation in clinical trials, 2 hospital pharmacists with experience in the assessment of orphan drugs and antiepileptic medicines (including DS) in Spain, 3 presidents of three DS Patient Associations, (100% parents of patients with DS), and 2 former national and regional decision-makers with wide experience in assessment of drugs both at European and Spanish level. Due to the COVID-19 pandemic, the study was carried out remotely, with a staged approach. The first step was an online meeting (held in early June 2020) in which participants received basic training on reflective MCDA methodology and the evidence matrices were presented. The second step (late June 2020) consisted of individual and remote scoring by study participants of the value framework criteria and reflection by themselves on the rationale behind the scoring. The final step was an online expert panel meeting (July 2020) in which results were presented and discussed as a group.

2.5. Data analysis

Value scores for each criterion for the four evidence matrices were collected from each participant, transferred to a common database, and analyzed quantitatively with Microsoft Excel software. Results were calculated and shown to study participants in the form of mean, standard deviation (SD), and range of minimum and maximum scores. Results are shown as the percentage of experts who considered the drug to have a negative, neutral, or positive impact according to each contextual criterion definition. Comments and reflections behind expert's scores were analyzed and discussed qualitatively. To check the degree of consistency and replicability of the analysis, a retest was carried out with the participants after the meeting. For the present paper, authors have

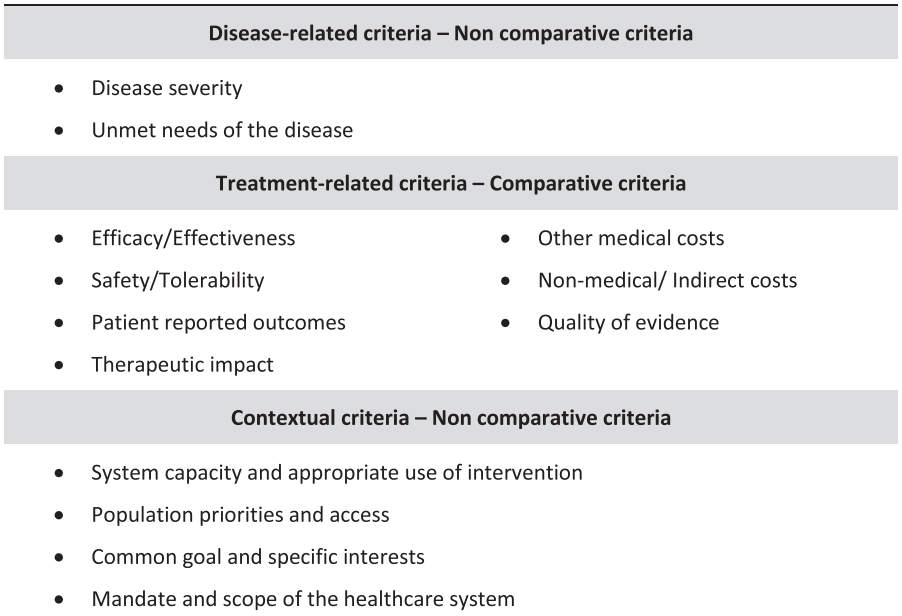

Fig. 1. MCDA Value Framework used in the study. Adapted from the ODs MCDA framework (Badia et al.) [40].

considered "similar" when compared scores were ≤±0.5; "slightly" lower/higher from ±0.6 to ±0.9 and "significantly" lower/higher when ≥±2.5.

3. Results

3.1. Literature review

A total of 433 publications were identified from biomedical databases (n = 402) and gray literature (n = 31). After withdrawal of duplicates, a total of 398 publications were selected of which, 114 publications were finally included. The remaining 284 publications were withdrawn based on title, abstract and/or full-text screening. The MCDA value framework was populated with data from 114 publications, as represented on a PRISMA flow diagram [44] in Fig. 2.

3.2. Performance scores and participant insights

Scores for the relative value contribution of fenfluramine compared with each of the four alternatives are shown in Fig. 3 (vs. stiripentol), Fig. 4 (vs. cannabidiol), Fig. 5 (vs. clobazam), and Fig. 6 (vs. topiramate). In all figures, dots correspond to the mean, while bars show the SD. Fig. 7 shows scoring results for contextual (qualitative) criteria.

3.2.1. Non-comparative criteria

3.2.1.1. Disease severity. Dravet syndrome is perceived as a very severe disease (4.6 ± 0.5), reflecting experts' perception of its impact on mortality, morbidity, and the impact on patients' and caregivers' QoL. All participants assigned a high score value (60% assigned the highest score (5)) to this criterion with a high degree of consensus. Participants justified their scores based on their understanding that DS is a complex, heterogenous, and unpredictable disorder, that begins in childhood, therefore affecting a highly vulnerable population, and associated with an increased risk of early mortality. It was also highlighted that DS is associated with a broad set of comorbidities resulting in severe cognitive and motor disabilities and behavioral problems.

3.2.1.2. Unmet needs. All participants (100%) considered that there are currently many and relevant unmet needs in DS (4.4 ± 0.7). Key unmet needs included 1) the modest efficacy of available ASMs (used in monotherapy or in combination) to control seizures, resulting in patients requiring additional non-pharmacological therapies (e.g. cognitive/behavioral, physiotherapy, vagus nerve stimulation therapy, and ketogenic diet); 2) problems associated with the safety profile of current ASMs: some may exacerbate seizures (e.g. lamotrigine) or cause central nervous system adverse events (AEs) (e.g. somnolence, drowsiness, ataxia, gait instability, and falls as well as mental slowing); and 3) the lack of alternatives with a positive impact on associated comorbidities and on QoL. Study participants believe that DS has a considerable impact on families leading to work and school absenteeism, as well as causing emotional disabilities such as anxiety, stress, and social isolation.

3.2.1.3. Therapeutic impact. The therapeutic impact of fenfluramine is considered very relevant (3.2 ± 1.3). The experts provided the following rationale for their score: 1) while several ASMs to treat seizures are available, DS clinical objectives are not completely met; 2) fenfluramine has demonstrated efficacy in preventing a wide range of convulsive (tonic, tonic-clonic, hemiclonic and focal seizures with an observable motor component) and non-convulsive seizures associated with DS; 3) it decreases seizure frequency, provides seizure-free periods and minimizes *status epilepticus* episodes; 4) fenfluramine provides seizure control in patients with currently uncontrolled DS with ASM regimens, who continue to experience a high burden of intractable seizures; 5) it can contribute to reducing the risk of mortality in patients with DS. Clinicians particularly highlighted that fenfluramine prevents

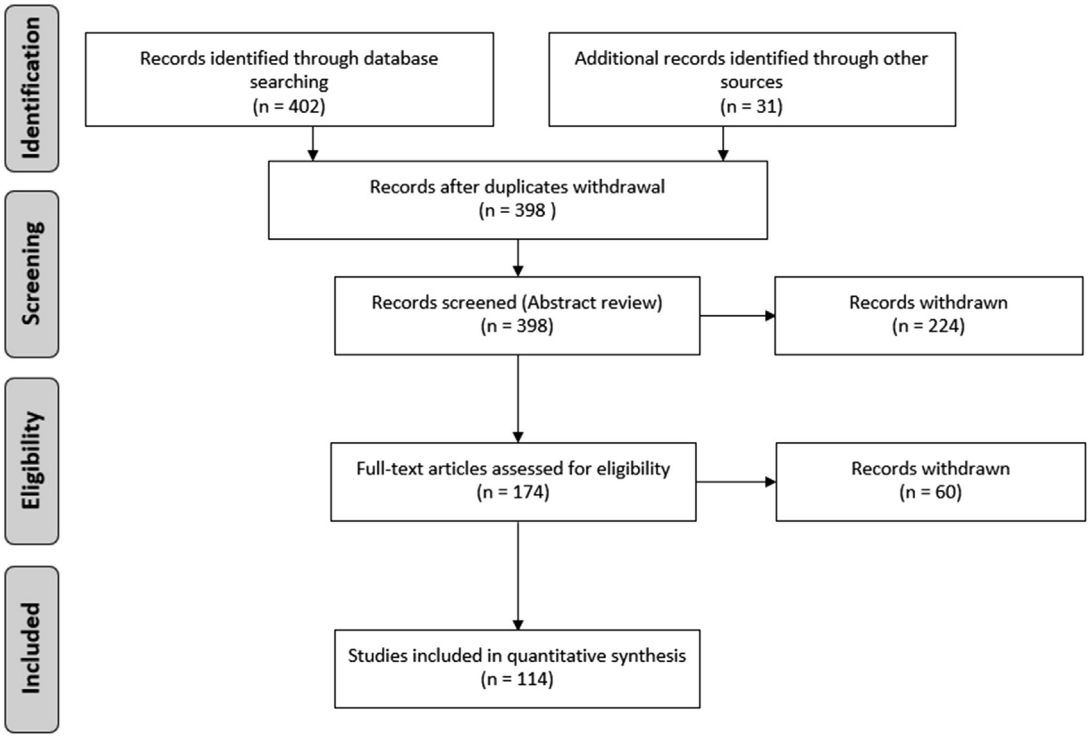

Fig. 2. PRISMA diagram [44] of the conducted literature review.

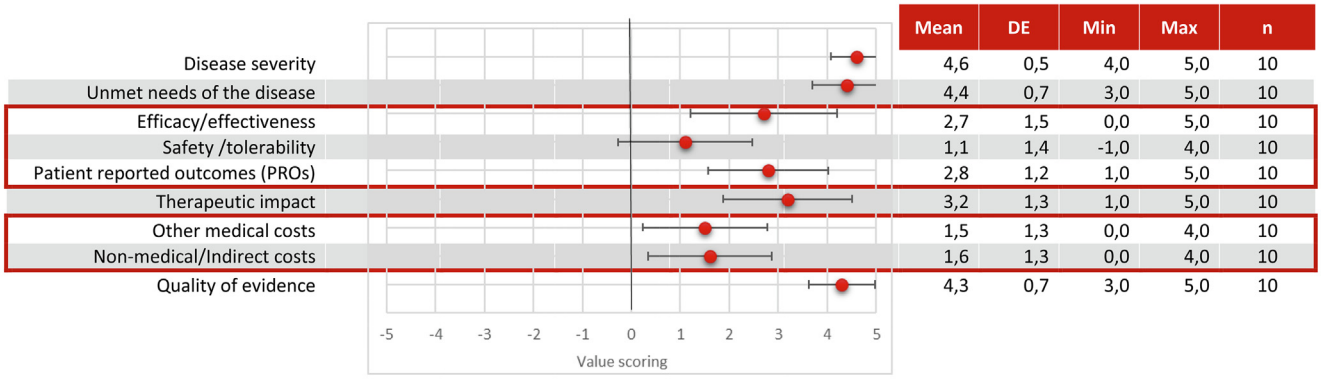

Fig. 3. Quantitative criteria value scoring results – fenfluramine vs stiripentol. Dots correspond to the mean of the scores assigned by study participants; bars show the SD. A constructed, cardinal scoring scale was used, ranging from 0 to 5 for non-comparative and from −5 to 5 for comparative criteria, respectively.

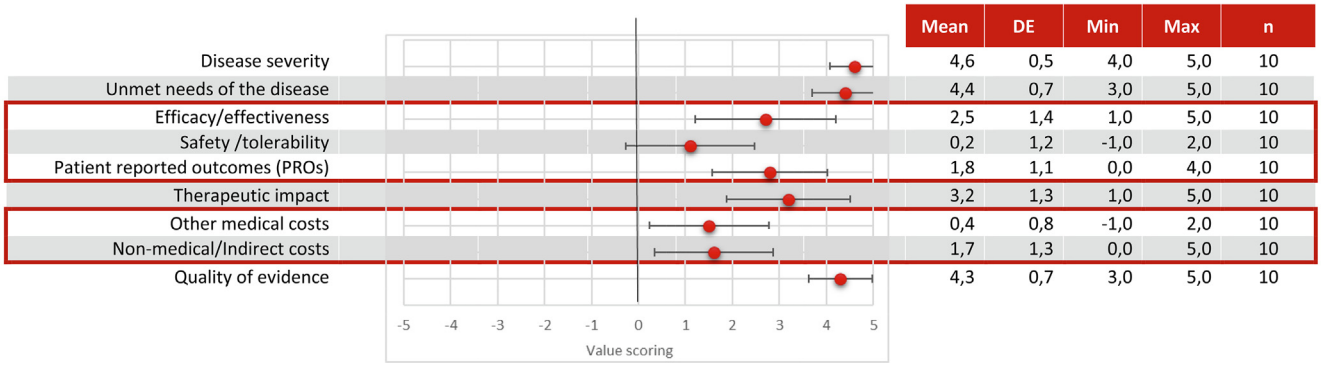

Fig. 4. Quantitative criteria value scoring results – fenfluramine vs cannabidiol. Dots correspond to the mean of the scores assigned by study participants; bars show the SD. A constructed, cardinal scoring scale was used, ranging from 0 to 5 for non-comparative and from −5 to 5 for comparative criteria, respectively.

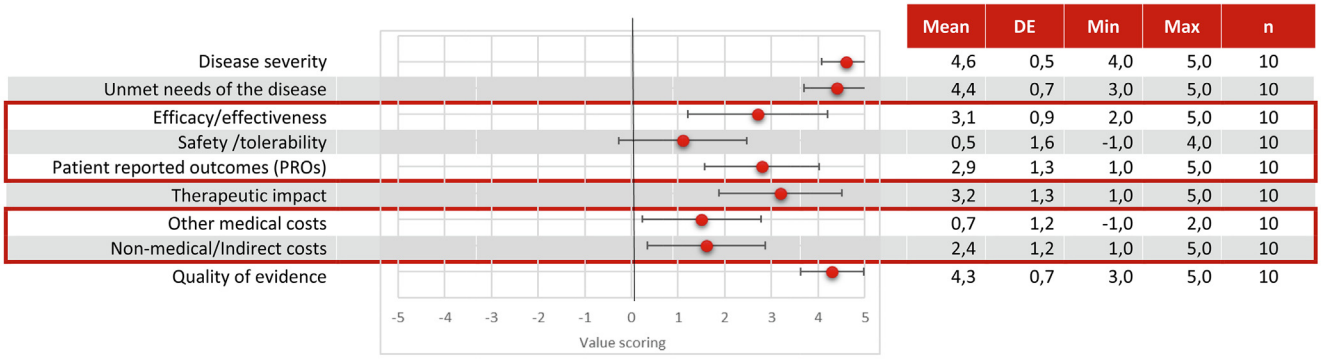

Fig. 5. Quantitative criteria value scoring results – fenfluramine vs clobazam. Dots correspond to the mean of the scores assigned by study participants; bars show the SD. A constructed, cardinal scoring scale was used, ranging from 0 to 5 for non-comparative and from −5 to 5 for comparative criteria, respectively.

convulsive generalized tonic-clonic seizures, associated with the risk of SUDEP, and that its efficacy in seizure control could lead to improvement in cognitive abilities and QoL in pediatric patients with DS, with a positive effect on caregivers'/parents' QoL.

3.2.1.4. Quality of evidence. All (100%) study participants considered that the regulatory approval of fenfluramine is supported by high-quality evidence (4.3 ± 0.7) derived from a robust clinical development program, including clinical endpoints relevant to the targeted indication and with strong study results. The experts highlighted that the studies were designed in accordance with the EMA's "Guideline on Clinical Investigations of Medicinal Products in the Treatment of Epileptic Disorders" (July 2010) [45], and that study results have been published in peer-reviewed journals [28–30].

The availability of long-term efficacy data for fenfluramine was highly valued by participants in comparison to the lack of equivalent data for, clobazam, stiripentol, and topiramate.

3.2.2. Comparative criteria

3.2.2.1. Efficacy–effectiveness. Compared with stiripentol (Fig. 3), fenfluramine has a significantly higher efficacy/effectiveness

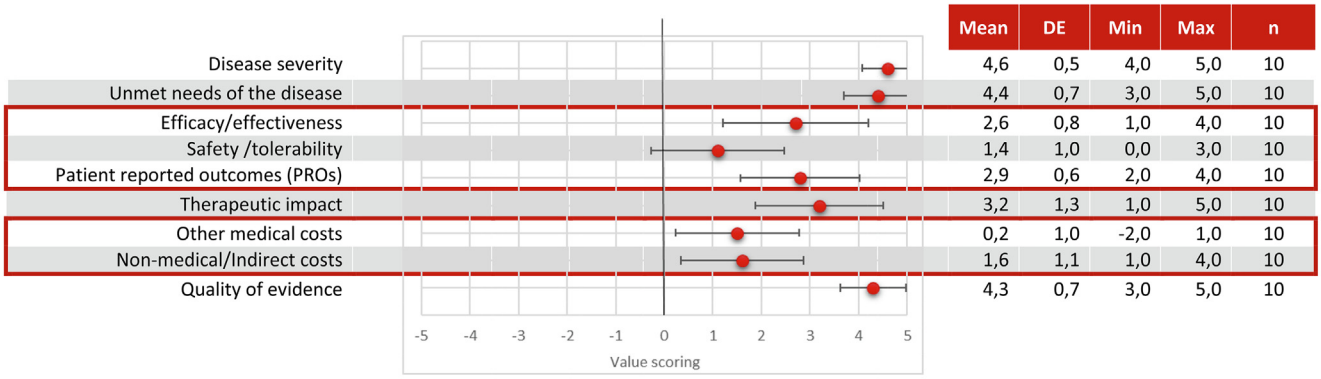

Fig. 6. Quantitative criteria value scoring results – fenfluramine vs topiramate. Dots correspond to the mean of the scores assigned by study participants; bars show the SD. A constructed, cardinal scoring scale was used, ranging from 0 to 5 for non-comparative and from −5 to 5 for comparative criteria, respectively.

(2.6 ± 1.4) in controlling multiple seizure types, even in patients with DS treated with a stable ASM regimen including stiripentol who continue to experience clinical burden from uncontrolled seizures: 1) clinical studies of stiripentol evaluated fewer convulsive seizure types (restricted to generalized tonic or tonic-clonic seizures) and not tonic-atonic, hemiclonic, and focal seizures with an observable motor component or non-convulsive seizures, as studied in fenfluramine randomized clinical trials (RCTs); 2) the experts highlighted the lack of published evidence on the long-term efficacy of stiripentol in pediatric patients, whereas, after an additional 24 months of treatment, fenfluramine demonstrated long-term durability of effect without development of tolerance [30]; 3) the clinical development program for fenfluramine appears more comprehensive than that of stiripentol, with evidence in patients taking different combinations of ASMs concomitantly. In addition, most patients in fenfluramine RCT had already failed to previous treatment with stiripentol, representing a more "refractory" patient group; 4) the seizure-free periods observed with fenfluramine have not been observed with stiripentol; 5) participants perceived that the great efficacy of fenfluramine in seizure control could contribute to improving other comorbidities associated with DS (e.g. cognitive disabilities and behavioral problems).

When compared with cannabidiol (Fig. 4), fenfluramine is considered by study participants to have a significantly higher efficacy/effectiveness (2.5 ± 1.4) because 1) fenfluramine has demonstrated efficacy in a greater percentage of patients than cannabidiol; 2) all fenfluramine groups were shown to have higher placebo-adjusted odds ratio (OR) of a clinically meaningful (≥50%) response rate (OR = 15 [4.5–50]) and (OR = 26 [5.5–123.2]) for fenfluramine 0.7 mg and 0.4 mg, respectively, vs. [OR = 2.74 (1.32–5.70)] and (OR = 2.21 [1.06–4.62]) for cannabidiol 20 mg and 10 mg, respectively) and profound (≥75%) response rates (OR = 55.1 [6–526]) and (OR = 23.7 [2.9–191.8]) for fenfluramine 0.7 mg and 0.4 mg, respectively, vs. (OR = 3.33 [1.01–10.92]) and (OR = 6.63 [2.12–20.73]) for cannabidiol 20 mg and 10 mg, respectively) [28,29,46,47]; 3) the clinical development of fenfluramine provides long-term efficacy evidence after an additional 24 months of fenfluramine treatment (median monthly convulsive seizure frequency (MCSF) for all subjects was 6, which represented a highly statistically significant reduction of −63.6% [$P < 0.001$]) from baseline [30], demonstrating the long-term durability of effect without the development of tolerance or waning, in contrast to the limited long-term evidence for cannabidiol, which has only been shown in pediatric patients after an additional 3 months of treatment (the median reduction in MCSF from baseline was −37.5%) [48]; 4) fenfluramine has demonstrated efficacy in multiple types of seizure: convulsive, – generalized tonic-clonic, tonic-clonic, tonic-atonic, hemiclonic, and focal with an observable motor component–and non-convulsive seizures, while cannabidiol studies evaluated fewer types of convulsive seizures (tonic, clonic, tonic-clonic, and atonic seizures).

Compared with clobazam (Fig. 5), it was considered that fenfluramine has a significantly higher efficacy in seizure control and without development of long-term tolerance (3.1 ± 0.9) due to 1) in clobazam epileptic encephalopathy trials only 16 (16.5%) patients treated had at least 50% decrease in seizures [49]; 2) experts also pointed out that clobazam had been studied in conjunction with other ASMs in patients with drug-resistant epilepsy or epileptic encephalopathy and not in DS, and therefore the long-term efficacy of clobazam in DS has not been demonstrated in clinical studies; 3) clobazam's clinical trials evaluated fewer types of convulsive seizures (generalized, focal, and undetermined seizures only) than those evaluated in fenfluramine studies and included an older pediatric population (from 6 years old vs from 2 years old with fenfluramine); 4) clinicians mentioned that, in real clinical practice, clobazam's efficacy is limited in the control of partial and absence seizures (rescue medication), highlighting the short durability of clobazam's effect, with development of tolerance in patients with DS and the lack of pediatric dosage forms.

Finally, when compared with topiramate (Fig. 6), fenfluramine was perceived to have a significantly higher long-term efficacy in seizure control (2.6 ± 0.8) because: 1) topiramate studies assessed less types of seizures (generalized tonic-clonic, partial -mainly partial motor- seizures, atypical absences and myoclonic seizures); 2) some inconsistencies were identified in the data from the topiramate studies with regards to response rates [50–52], questioning, therefore, results validity; and 3) the design of fenfluramine studies was considered more rigorous, less prone to bias and better reflecting current state-of-the-art requirements.

3.2.2.2. Safety/tolerability. Compared with stiripentol, study participants considered that fenfluramine shows a better safety/tolerability profile (1.1 ± 1.4). All experts expressed great difficulty in comparing the safety/tolerability of fenfluramine *versus* stiripentol since they considered it is not possible to discern AEs specifically attributed to the treatments or associated with the clinical features of DS, such as food intake problems. Participants highlighted that the clinical development program of stiripentol did not include long-term safety in pediatric patients, and that the small sample size may have precluded identification of infrequent or rare AEs. In contrast, the safety profile of fenfluramine is consistent across RCTs and the OLE study: no patients experienced valvular heart disease (VHD) or pulmonary arterial hypertension (PAH), and the reported AEs are considered manageable and measurable. Also,

and despite being an anorectic agent, treatment with fenfluramine did not lead to discontinuation due to weight loss in any case.

Fenfluramine's safety/tolerability profile is considered similar to cannabidiol (0.2 ± 1.2) while slightly superior to clobazam (0.5 ± 1.6). Clinicians mentioned uncertainty on cannabidiol's long-term safety profile with regard to potential toxic hepatitis due to reported transaminase elevations, although this is reported more often in patients with DS receiving concomitant valproic acid.

Compared with topiramate, fenfluramine was considered to have a better safety/tolerability profile (1.4 ± 1.0) on the basis of AEs associated with topiramate in real clinical practice: e.g. hypohidrosis/hyperthermia (seizure trigger) and increased cognitive problems [14].

3.2.2.3. Patient reported outcomes (PROs). Patient QoL outcomes were considered to be better studied in the fenfluramine's clinical development program than in those for the other four ASMs, providing evidence through different Observer-Reported Outcome (ObsRO) Measures, including the use of HRQoL questionnaires in pediatric patients with DS: 1) the clinical global impression-improvement (CGI-I) scale (measuring overall assessment of benefit, safety, and tolerability beyond seizure reduction or safety/tolerability by the parent/caregiver and investigator), and 2) the Pediatric QoL scale (PedsQL), (measuring physical, emotional, social, and school functioning). These QoL measures capture the overall health status of patients with DS and the impact of comorbidities associated with the disease (e.g. cognitive and motor functioning).

Fenfluramine was considered to have a significantly better impact on patients' QoL than stiripentol (2.7 ± 1.4), as it improves patient's QoL in CGI-I sores, even in those patients who were experiencing a higher seizure burden despite being treated with stiripentol-containing regimens. Fenfluramine improves executive functions (measured by the Behavior Rating Inventory of Executive Function (BRIEF) scale, within the context of everyday functioning in children), whereas stiripentol usually causes hyperexcitability and drowsiness, which could have a negative impact on executive functions.

All participants considered that fenfluramine has a better (1.8 ± 1.1) impact on patient's QoL than cannabidiol based on data from RCTs and self-experience: more subjects treated with fenfluramine were rated as "Clinically Meaningfully Improved" using the CGI-I scale studies.

When compared with clobazam and topiramate, experts found fenfluramine as significantly superior in terms of impact on QoL (2.9 ± 1.3 and 2.9 ± 0.6, respectively). Based on clinicians' experience, clobazam is associated with somnolence, hyperactivity and inattention, with a negative impact on patients' (e.g. learning problems at school) and caregivers' QoL. AEs (e.g. hypohidrosis and cognitive problems) associated with topiramate may also have a negative impact on patients' and caregivers' QoL. Besides, topiramate studies did not provide evidence on QoL in pediatric patients with DS.

All participants considered that fenfluramine will have a positive impact on important comorbidities (such as severe cognitive and motor disabilities, behavioral problems, speech impairment, autism spectrum symptoms, and attention-deficit/hyperactivity disorder), contributing to improving patients' and caregivers' QoL.

3.2.2.4. Other medical costs (excluding pharmacological costs). The higher efficacy and acceptable safety and tolerability profiles of fenfluramine may have a significant and positive impact on reducing other medical costs associated with treatment of patients with DS (e.g. avoiding and/or reducing A&E visits, ambulance calls, specialist visits, physiotherapy, cognitive/behavioral therapy, adverse event management costs, and long-term care costs) in relation to the comparators used in this study.

Other medical costs were considered lower for fenfluramine in comparison to stiripentol (1.5 ± 1.3). Although treatment with fenfluramine includes monitorization costs (i.e. performing an echocardiogram to evaluate for potential regurgitant aortic or mitral valvular heart disease [19]), monitorization costs for stiripentol are higher (i.e. child liver function and blood counts and plasma concentration measurements and potential risk of overdose [54]).

Cannabidiol was considered to be associated with slightly higher costs than fenfluramine (0.4 ± 0.8) given the need for clinical monitoring of serum transaminases and total bilirubin levels to evaluate for liver function and the need to monitor plasma concentrations during concomitant treatment with other ASMs [15].

Clobazam was considered to be associated with slightly higher costs when compared with fenfluramine (0.7 ± 1.2), limited due to the need for monitorization of plasma concentrations during clobazam treatment because of drug interactions [12].

Although the medical costs of fenfluramine were considered similar to those of topiramate (0.2 ± 1.7), experts noted that patients treated with topiramate often require neuropsychological assessment due to its negative effects on cognitive functions [14], leading to additional costs. Fenfluramine's efficacy in seizure control and preserving cognitive functions could have a positive impact on reducing other medical costs in comparison to topiramate.

3.2.2.5. Non-medical/indirect costs. Participants considered that fenfluramine treatment has a positive impact on non-medical/indirect costs when compared with stiripentol (1.6 ± 1.3), cannabidiol (1.7 ± 1.3), clobazam (2.4 ± 1.2), and topiramate (1.6 ± 1.1). Fenfluramine's greater efficacy in seizure control and prolongation of seizure-free periods may contribute to maintaining patient autonomy, increasing parents' productivity, and reducing out-of-pocket-related expenses. Its positive impact on patients' and relatives' QoL could reduce the financial burden on social services.

3.3. Qualitative (contextual) criteria results

Scoring results from qualitative criteria are shown in Fig. 7.

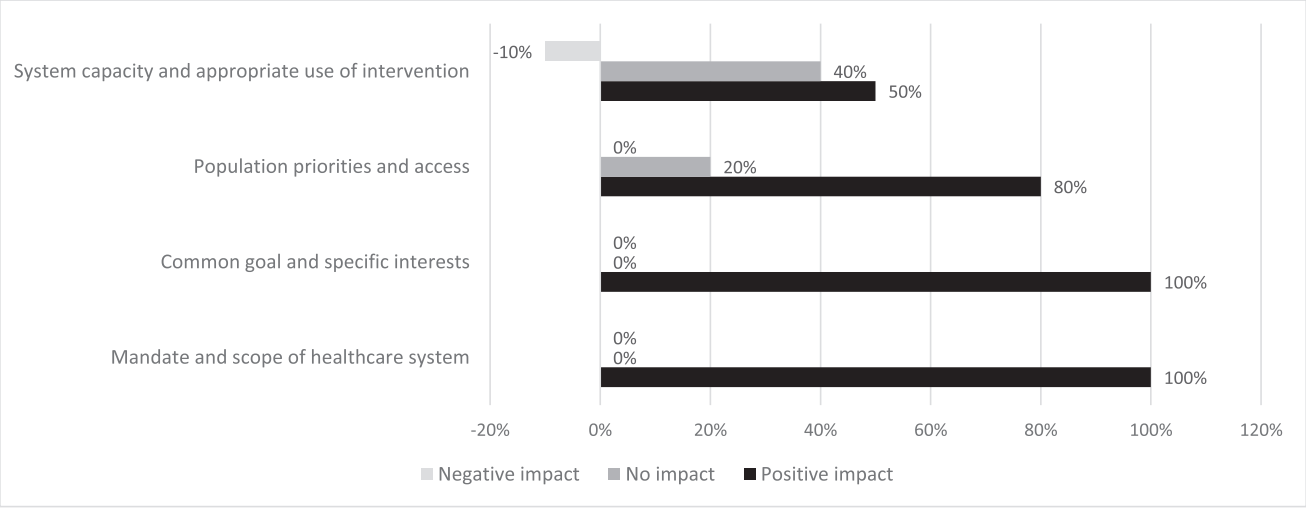

Fig. 7. Percentage of participants who considered that the incorporation of fenfluramine for the treatment of DS in Spain would have some type of impact with respect to the contextual criteria of the adapted MCDA framework.

3.3.1. System capacity and appropriate use of intervention

Most experts (90%) consider fenfluramine as a new therapeutic option for patients with DS that can be perfectly incorporated and used within the Spanish NHS. The rest (10%) of participants expressed some concerns about the safety monitoring measures (i.e. electrocardiograms (ECGs)) required before and during treatment with fenfluramine. However, all participants agreed that its introduction in the Spanish NHS will not require additional organizational or training resources since ECGs are routinely used in healthcare centers.

3.3.2. Population priorities and access

The majority (80%) of participants considered fenfluramine to be fully aligned with the health priorities in this patient population, contributing to the achievement of the objectives and health outcomes reflected in clinical guidelines, and fulfilling a clear unmet need in a patient population that starts in the pediatric age. Participants who considered that the introduction of fenfluramine into the Spanish healthcare system would have a neutral impact (20%) explained their score on the basis that the patient population is currently very small and that, collectively, is currently under-represented in strategic healthcare plans.

3.3.3. Common goal and specific interests

All participants (100%) agreed that the availability of fenfluramine would be completely aligned with the objectives and specific interests of patients with DS and the physicians treating them.

3.3.4. Mandate and scope of healthcare system

All participants (100%) considered that the use of fenfluramine would be aligned with the mandate and scope of the Spanish NHS, as it is indicated to treat a rare disease with a major pediatric component.

4. Discussion

The relative value contribution of fenfluramine, in comparison with the currently used therapeutic alternatives (clobazam, stiripentol, and topiramate) and a recently approved treatment but not yet available in Spain at the time of study (cannabidiol), was assessed using reflective MCDA methodology.

Dravet Syndrome is perceived as a severe disease with high unmet needs and associated with high morbidity and mortality that can occur at any age but specially during childhood [6,7]. There is a great need to improve the early diagnosis of DS, permitting for the timely instauration of optimal treatment as early as possible. In addition, more effective treatments are needed to effectively control seizures positively impacting on DS comorbidities and thereby improving patients' and caregivers' quality of life. The results of this study suggest that fenfluramine may represent a suitable alternative in this rare disease in urgent need of more effective treatments. When compared with the alternatives, fenfluramine is perceived as a drug with better efficacy in controlling multiple seizure types (including generalized tonic-clonic, which are considered a major risk of SUDEP [7,53–55]), even in patients treated with a stable ASM regimen containing stiripentol, who are not eligible to stiripentol or stiripentol-experienced patients who still experience a high burden of uncontrolled seizures.

Special mention must be made of the comparison of fenfluramine *versus* cannabidiol in light of its recent approval and availability in Spain. Based on their development program and Summary of Product Characteristics (SmPCs) [15,18], both products are expected to be positioned similarly within the current clinical practice algorithm in Spain as a second line "add-on" treatment [56]. During the MCDA exercise, fenfluramine was perceived by experts as more efficacious than cannabidiol. These results are in line with a recently conducted indirect treatment comparison (ITC) between both treatments (not available at the time of the present study) in which fenfluramine showed greater efficacy than cannabidiol in a comparable population [57].

The reflective component of the MCDA methodology used in this study contributed to understanding and discussing the rationale behind experts' scores for each value criterion. The study could contribute to support decision making by providing a comprehensive exploration of the in-depth quantification and analysis of the aspects underlying the positive perception of the value contribution of fenfluramine to the treatment of DS in Spain. It is therefore understandable that MCDA is becoming increasingly popular to support healthcare decision-making, particularly in complex cases such as ODs indicated for treatment of rare diseases [35,37,58].

In DS, as for other rare diseases, the decision for choosing a treatment not only depends on clinical experience, patient charac-

teristics, and caregivers' preferences, but also depends on treatment availability [59]. Fenfluramine is currently undergoing pricing and reimbursement assessment in Spain and cannabidiol underwent a lengthy process. In Europe, there are some inequities in terms of timing and level of access to new treatments, particularly in the area of orphan drugs [60]. In fact, as reported in the W.A.I.T Survey report (2021) [61] developed by European Federation of Pharmaceutical Industries and Associations only the 34% of all orphan drugs approved by the EMA are available in Spain (EU average 41%) with a mean delay of 665 days from the EMA marketing authorization to effective access through the inclusion in the Spanish reimbursed list, far behind other EU countries such as Germany, Italy, France, or Austria.

One of the strengths of this study is that it involved a multidisciplinary group of experts, including the patient's perspective, hence enriching the results and the conclusions that can be derived from it. Each criterion was evaluated in a transparent and objective manner, also providing and considering a contextual tool for analysis following a well-established, accepted, and consolidated methodology. Another additional strength is that, to the authors' knowledge, this study represents the first study to apply MCDA methodology to determine the value contribution of a treatment option for DS in Spain.

The study has some limitations. The results depend to some extent on the composition of the expert panel, on their value judgements, and experience. To mitigate the risk of expertise bias, training on MCDA methodology was provided to all participants prior to the individual scoring work and discussion session. Other study limitations are the lack of information/data available at the time as well as the differences in patient populations studied with each treatment alternative. Therefore, the results may change when new data become available, which warrants a follow-up of this study.

The study participants represented the key profiles in decision-making and the size of the group is representative, and in some cases exceeds, the size of real-life drug evaluation committees in Spain. It is also similar to that of other MCDA exercises [37,62–66]. However, it could benefit from being replicated with experts from other Spanish hospitals and regions.

5. Conclusions

The results show the high added value of fenfluramine as a DS treatment from a multidisciplinary perspective, under a methodological umbrella that takes into account a broad spectrum of value attributes.

Reflective MCDA has been proven to be a useful tool to help make informed decisions regarding new treatment options.

This MCDA study results could contribute to take healthcare policies to the next level of excellence by understanding how value in DS is defined and recognized by patients, clinicians, and decision-makers in Spain, informing the development of new, future therapeutic alternatives for this indication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr Gil-Nagel reports consultancy or speakers' honoraria from Eisai, UCB, GW Pharma, Esteve, Zogenix and Stoke Therapeutics, Angelini Pharma and Biocodex. He has been an investigator for GW pharma, Zogenix, UCB and Takeda. Dr Falip has received honoraria for advisory boards/consultancy and speaking fees from UCB Pharma, ESAI, Esteve, Bial, Zogenix, GW Pharmaceuticals and Livanova. Dr. Sánchez-Carpintero has received honoraria for advisory boards from GW Pharmaceuticals and Zogenix; she has been an investigator for GW Pharmaceuticals Zogenix and Takeda and has received speaking fees from Biocodex, GW Pharmaceuticals, and Zogenix. Dra Abad-Sazatornil has received speakers' fees from Janssen, Sobi, Galapagos, Abbvie, Ipsen, Biogen. JAA is a president of Dravet Syndrome Foundation Spain (DSF). He and/or DSF have received grants and/or financial support from GW Pharma, Zogenix, Ovid Therapeutics, Encoded Therapeutics, Biocodex, Praxis, and StrideBio to help carry out some of the DSF's foundational activities or provide consulting services. JAA honoraria has always been directly or indirectly donated to DSF. Dr Sancho-López has received honoraria for consultancy services from Angelini Pharma. Dr. Trillo-Mata has received honoraria for advisory boards from Arvelle Therapeutics, Zogenix International Ltd, GW Pharma Limited. No other potential conflicts of interest are reported.

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