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Value contribution of cenobamate for the treatment of Focal-Onset Seizures (FOS) in patients with drug-resistant epilepsy (DRE) in Spain through reflective Multi-Criteria Decision Analysis (MCDA)

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ABSTRACT

Introduction: Epilepsy is one of the most common neurological conditions worldwide. The main goal of its treatment is to achieve seizure freedom without intolerable adverse effects. However, despite the availability of many anti-seizure medications, including the latest options, called third-generation anti-seizure medications (ASMs), approximately 40% of people with epilepsy present drug-resistant epilepsy (DRE). Cenobamate is the first ASM approved in Spain for the adjunctive treatment of Focal-Onset Seizures (FOS) in adult patients with DRE. In a chronic disease with a portfolio of available ASMs, the decision to introduce a new therapeutic alternative must follow a holistic evaluation of value provided. Reflective Multi-Criteria Decision Analysis (MCDA) methodology allows to determine the value contribution of a treatment in a given indication considering all relevant criteria for healthcare decision-making in a transparent and systematic manner from the perspective of relevant stakeholders.
Purpose: The aim of this study was to determine the relative value contribution of cenobamate in the treatment of FOS in patients with DRE compared with third-generation ASMs using reflective MCDA-based methodology.
Methods: A systematic literature review (combining biomedical databases and grey literature sources) was performed to populate the Evidence and Value: Impact on DEcisionMaking (EVIDEM) MCDA framework adapted to determine what represents value in the management of FOS in patients with DRE in Spain. The study was conducted in two phases. The first took place in 2021 with a multi-stakeholder group of eight participants. The second phase was conducted in 2022 with a multi-stakeholder group of 32 participants. Participants were trained in MCDA methodology and scored four evidence matrices (cenobamate vs. brivaracetam, vs. perampanel, vs. lacosamide and vs. eslicarbazepine acetate). Results were analyzed and discussed in a group meeting through reflective MCDA discussion methodology.
Results: DRE is considered a very severe condition associated with many important unmet needs, mainly with regard to the lack of more effective treatments to achieve the ultimate goal of treatment. Compared to third-generation ASMs, cenobamate is perceived to have a better efficacy profile based on improvements in responder rate and seizure freedom. Regarding safety, it is considered to have a similar profile

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to alternatives and a positive quality-of-life profile. Cenobamate results in lower direct medical costs (excluding pharmacological) and indirect costs. Overall, cenobamate is regarded as providing a high therapeutic impact and supported by high-quality evidence.
Conclusions: Based on reflective MCDA methodology and stakeholders' experience in clinical management of epilepsy in Spain, cenobamate is perceived as a value-added option for the treatment of patients with DRE when compared with third-generation ASMs.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders with a global prevalence of almost 50 million [1,2]. According to a Spanish systematic review, the prevalence of active epilepsy in adults in Spain has been estimated at 5.79 per 1,000 persons [3], which corresponds to approximately 200,000 adult patients. Epilepsy is characterized by recurrent spontaneous seizures which can be classified as focal or generalized. Focal-Onset Seizures (FOS) represents the most common type in the adult population, accounting for more than 60% of patients with epilepsy in Spain [4].

Medical therapy for epilepsy is based on long-term administration of oral anti-seizure medications (ASMs) [5] with the aim of achieving seizure freedom without causing side effects. The overall prognosis of epilepsy is favorable in most patients when measured by occurrence of seizure freedom. However, approximately 40% of patients, particularly those with FOS, continue to experience uncontrolled seizures despite treatment with at least two ASMs (in monotherapy or in combination) [6], which is known as drug-resistant epilepsy (DRE) according to the International League Against Epilepsy (ILAE) [7].

DRE is considered a severe condition associated with a significant decrease in quality of life (QoL) for patients and their caregivers, the presence of associated comorbidities and an increased probability of early death compared with patients with controlled epilepsy [8]. DRE involves greater use of resources and places a considerable burden on the National Health System (NHS) and society in general [8–10].

Adequate DRE management is associated with relevant unmet needs, mainly the availability of alternative ASMs with improved efficacy and tolerability profiles that allow to reach treatment objectives [8]. Despite the existing portfolio of more than 20 ASMs for the treatment of FOS, including the most recent ASMs approved in the last decade, the so-called 'third-generation ASMs', the probability of achieving seizure freedom has not been substantially modified compared to previous years, remaining at approximately 4% in the pivotal studies (or for DRE) [6,11]. However, third-generation ASMs are considered to be better tolerated and present less drug-drug interaction than older drugs, being the most commonly used options in DRE patients. There is no specific clinical protocol for the use of ASMs in DRE, and treatment choice should be individualized according to the patient's profile, making the choice of medication difficult [12].

Cenobamate represents the first ASM approved and commercialized in Spain [13], indicated for the adjunctive treatment of FOS in adult patients with epilepsy who have not been adequately controlled despite a history of treatment with at least two ASMs [14]. Cenobamate has demonstrated high efficacy, with as much as a 20% rate of seizure-free patients, never reached before in comparable trials with other ASMs [15,16] representing a new efficacious treatment option for these patients [17]. As such, the Spanish Society of Neurology (SEN) has recently recognized cenobamate as the only effective treatment for DRE in its clinical practice guidelines [12].

Reimbursement decisions for new drugs usually represent a challenge for healthcare systems. In a chronic disease with a portfolio of available ASMs, the decision to introduce a new therapeutic alternative must follow a holistic evaluation of value provided, not limited to the traditional criteria of efficacy, safety and cost, and reflecting the diverse perspectives of key stakeholders. Reflective Multi-Criteria Decision Analysis (MCDA) methodology enables to perform a structured, comprehensive, and multidisciplinary analysis of the added global value of a drug compared to existing alternatives considering the perspectives of stakeholders involved in evaluation and decision-making [18,19].

Reflective MCDA methodology has been recently used to determine key value drivers in the treatment of FOS in patients with DRE, providing a standardized MCDA framework to aid stakeholders to assess the value contribution of any treatment directed to these patients [8].

The aim of this study was to determine the relative value contribution of cenobamate in the treatment of FOS in patients with DRE compared with third-generation ASMs using reflective MCDA-based methodology.

2. Methods

2.1. Study design

The study was designed following good practice recommendations for the application of MCDA methodology [18,19], using the Evidence and Value: Impact on DEcisionMaking (EVIDEM) MCDA framework specifically adapted to determine what represents value in the management of FOS in patients with DRE in Spain [8]. Third-generation ASMs (brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate) were selected as comparators since they represent the most commonly prescribed treatments in the same line of treatment as cenobamate (third-line adjunctive setting), accounting for, approximately, 70% of prescriptions in Spain [20].

A systematic literature review was conducted to obtain relevant information on the disease and its current management in Spain as well as relevant evidence for cenobamate and all comparators. Information was structured into four evidence matrices, according to each of four comparators. The matrices were scored by a representative, multidisciplinary panel of Spanish stakeholders involved in healthcare decision-making, including evaluators, physicians, and patient representatives. Scores were analyzed quantitatively. Comments and reflections behind experts' scores were collected in a qualitative manner.

2.2. Literature review

A systematic literature review [21,22] was performed between November and December 2020, and later updated until September 2022 to obtain relevant information about FOS in patients with DRE, including data on cenobamate and the four comparators: brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate.

The literature review was carried out according to a protocol including the criteria of the adapted EVIDEM MCDA framework [23]. Articles identified through the search were screened by title and abstract. Those articles falling outside the search objective or not meeting eligibility criteria were excluded. A full-text assessment was performed with those remaining. Articles not containing the elements required by the study objectives were excluded; those remaining were included in the study and thoroughly analyzed.

Published evidence was searched using the biomedical databases MEDLINE [24], Cochrane [25], and MEDES [26], and included articles in English and Spanish. It was complemented using grey literature sources such as Google Scholar, patient association websites, and available documents from official sources (e.g., European Medicines Agency (EMA), Agency of Medicines and Medical Devices (AEMPS), and Spanish regional and hospital drug evaluations).

2.3. Reflective MCDA tool and evidence matrices development

The MCDA framework used was the one adapted to determine what represents value in the management of FOS in patients with DRE in Spain, published in a recent Spanish study [8]. This adapted MCDA framework is based on the EVIDEM framework (version 4.0) [27] and composed of a total of 15 criteria (Table 1).

The information extracted from the literature review was used to populate the four MCDA evidence matrices to determine the value contribution of cenobamate in respect to each of the four third-generation ASMs for the treatment of FOS in adult patients with DRE in Spain. The "Non-comparative criteria" scoring scale ranged from 0 to 5 (where 0 is the worst possible score and 5 the best). Comparative criteria (efficacy/effectiveness, safety/tolerability, patient reported outcomes (PROs) and economic) were scored on a scale ranging from −5 (cenobamate much worse compared to the alternative) to +5 (cenobamate much better than the alternative). Contextual criteria were scored using a three-point qualitative scale: positive, neutral, or negative.

Direct comparisons could not be made for the 'cost of intervention' criterion, since cenobamate had not been reimbursed in Spain at the time of the study, and its price was not available. Therefore, this criterion was excluded from the framework.

For the phase 2 of the study (see Section 2.4), evidence matrices were updated with the new available evidence published up to September 2022, which includes indirect comparisons among the third-generation ASMs in terms of efficacy [28], safety [28], retention rate [29], and economic evaluation [20].

Table 1
MCDA adapted for evaluation of medicines indicated for the treatment of FOS in patients with DRE [8].

Quantitative criteria
Disease severity
Size of affected population
Unmet needs
Comparative efficacy / effectiveness
Comparative safety / tolerability
Comparative patient reported outcomes (PROs)
Type of therapeutic benefit
Comparative cost of intervention*
Comparative other medical costs
Comparative non-medical (indirect) costs
Quality of evidence
Expert consensus / clinical practice guidelines
Contextual criteria
Mandate and scope of healthcare system and population priorities and access
Common goal and specific interests
System capacity and appropriate use of intervention

*Criterion excluded from the framework.

2.4. Expert panel design and conduct of the study

A total of 40 participants were selected to represent relevant stakeholder profiles in epilepsy including physicians, evaluators, and patient representatives in order to collect insights from a broad range of perspectives and to achieve a widespread distribution across the Spanish territory. Physicians included neurologists with experience in the management and treatment of DRE patients. Evaluators included payers, hospital, and primary care pharmacists with experience in drug evaluation. All those participants come from public hospitals with the only exception of a neurologist from a private center located in Andalucia. Patient Representatives included two members of national patient associations on epilepsy (the Spanish Federation for Epilepsy (FEDE) and the National Association of People with Epilepsy (ANPE)).

The study was carried out in two separate phases.

- Phase 1 took place between January and February 2021 with involvement of eight participants: four evaluators and two physicians from four different Spanish regions (Andalusia, Catalonia, Community of Madrid, and Valencian Community) and two national patient representatives.
- Phase 2 took place between April and November 2022, during which the study was replicated in a broader sample of 32 participants, eight from each of four Spanish regions: Andalusia, Catalonia, Galicia, and Valencian Community. Participants included four evaluators and four clinicians from each of the regions. Patient representatives were excluded in phase 2 as they are not currently involved in regional drug evaluation and decision-making.

Due to the COVID-19 pandemic, the study was carried out remotely, with a staged approach in both phases. The first step was an online meeting in which participants received basic training on reflective MCDA methodology and were presented with the evidence matrices. The second step involved individual, remote scoring of the value framework criteria, and reflection of the rationale behind the scoring. The final step was an online expert panel meeting in which results were presented and reflectively discussed as a group. To facilitate participation in group discussions and sharing of perspectives for each participant, phase 2 was carried out as four separate sessions, one per region. In addition, this sample replicated the current size of drug evaluation committees at regional level and allowed to identify differences in scores between different regional contexts.

2.5. Data analysis

Results obtained from each phase of the study were analyzed separately, since they were conducted one year apart in time and the evidence matrices were updated between phase 1 and 2, with new evidence available during that period. Participant profiles involved in both study phases were different as described previously (see section 2.4).

For each study phase, data obtained were collected from each participant, transferred to a common database and analyzed with Microsoft Excel. Scores were analyzed quantitatively. For each criterion, the mean, the standard deviation (SD), and the range of scores (minimum and maximum) were calculated. Comments and reflections behind participant's scores were analyzed and discussed in a qualitative manner. For contextual criteria, grades were transformed to a numerical scale (Positive as + 1, Neutral as 0 and Negative as −1). Results are shown as percentage of experts who

would consider that the drug would have a negative, neutral, or positive impact, according to each contextual criterion definition.

A Mann-Whitney U test for impaired samples was performed to check the degree of consistency of results from both phases of the study and assess potential differences between them.

3. Results

Findings from the Mann-Whitney U test confirmed the consistency of mean scoring by participants from phase 1 and phase 2, except for the "safety/tolerability" criterion when compared to cenobamate vs brivaracetam, for which, scores from both phases of the study, were statistically significant ($p < 0.015$). Therefore, the differences in scoring for this criterion between the two phases are described individually. Since no significant differences in scoring between the two phases were found for the rest of criteria, these are described as a whole. Regarding phase 2, the results obtained are consistent across regions, so the results of the 32 participants are shown pooled.

Scores obtained for the non-comparative quantitative criteria of the evidence matrix are shown in Fig. 1. Scores for the comparative criteria of the evidence matrices (cenobamate vs third-generation ASMs) are shown in Fig. 2 (efficacy/effectiveness), Fig. 3 (safety/tolerability), Fig. 4 (PROs), Fig. 5 (other medical costs), and Fig. 6 (indirect costs). In all figures, the black and white dots correspond to the mean of the scores assigned by participants during phase 1 and phase 2, respectively, and the bars show the standard deviation (SD). Scoring differences across experts' profiles of both phases of the study are shown in the Supplementary Figures (Supp.).

Regarding the scoring of the contextual criteria, there were no major differences between profiles or between study phases. Fig. 7 shows pooled results of the contextual criteria scores from the total of 40 participants from both phases of the study.

3.1. Non-comparative criteria

3.1.1. Disease severity

DRE is perceived, with high consensus across stakeholders' profiles, as a very severe condition (phase 1: 4.4 ± 0.5; phase 2: 4.3 ± 0.6) (Fig. 1) due to its high risk of mortality (mainly sudden unexpected death in epilepsy (SUDEP)), and due to the increased risk of physical (injuries) and psychological (depression and anxiety) comorbidities, which leads to reduced health-related QoL of patients and their caregivers. In addition, all participants consider

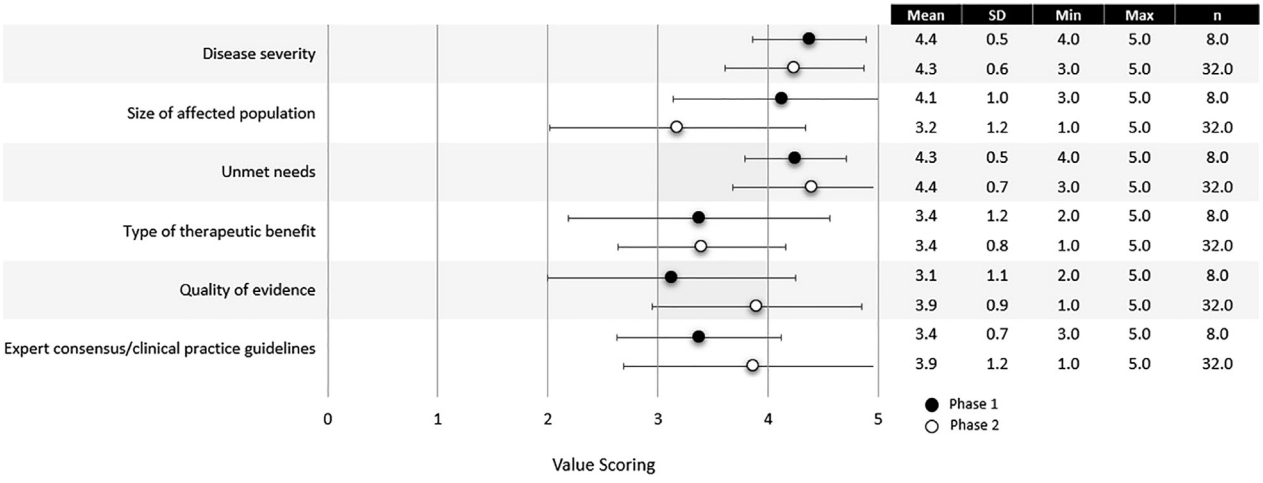


Fig. 1. Non-comparative quantitative criteria value scoring results: phase 1 and phase 2.

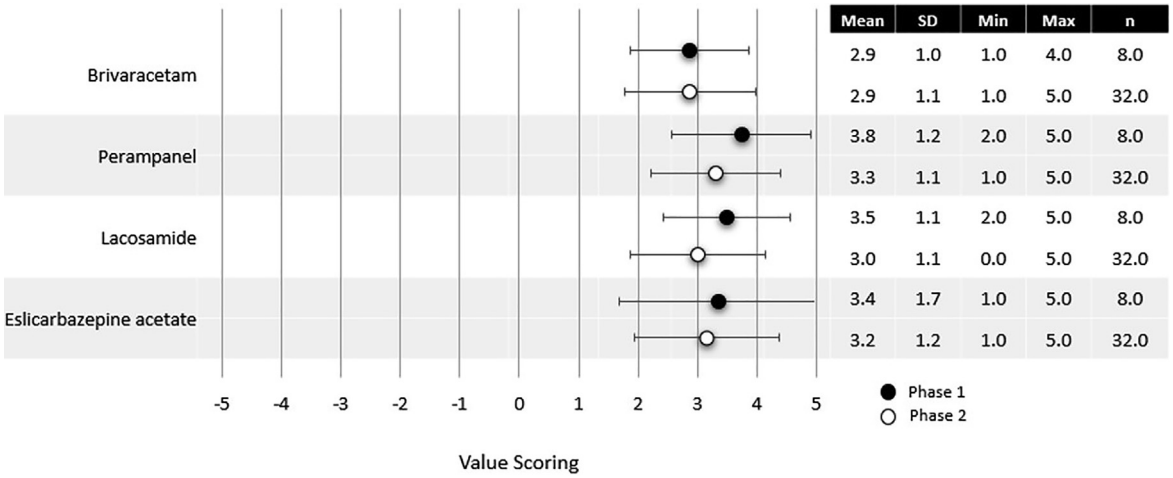
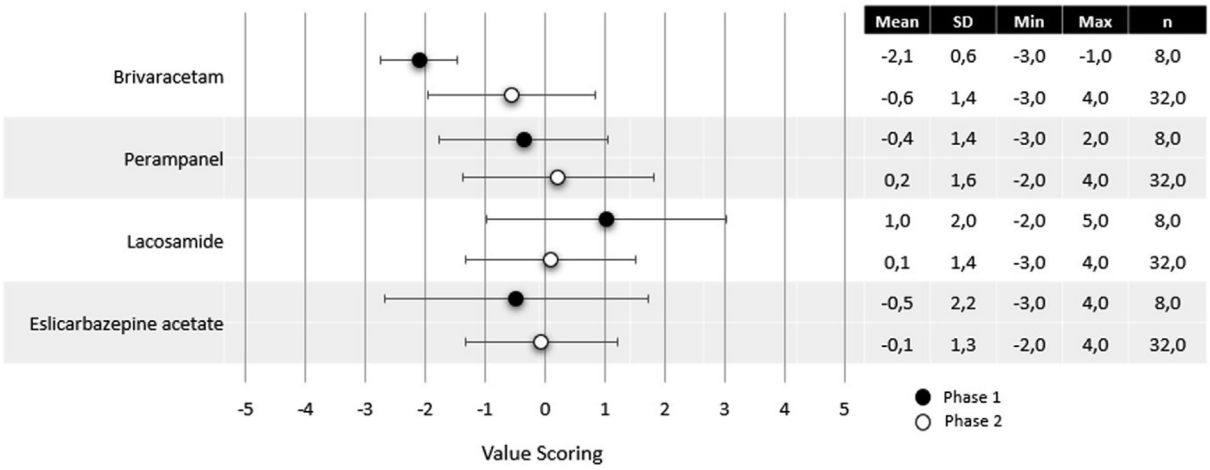
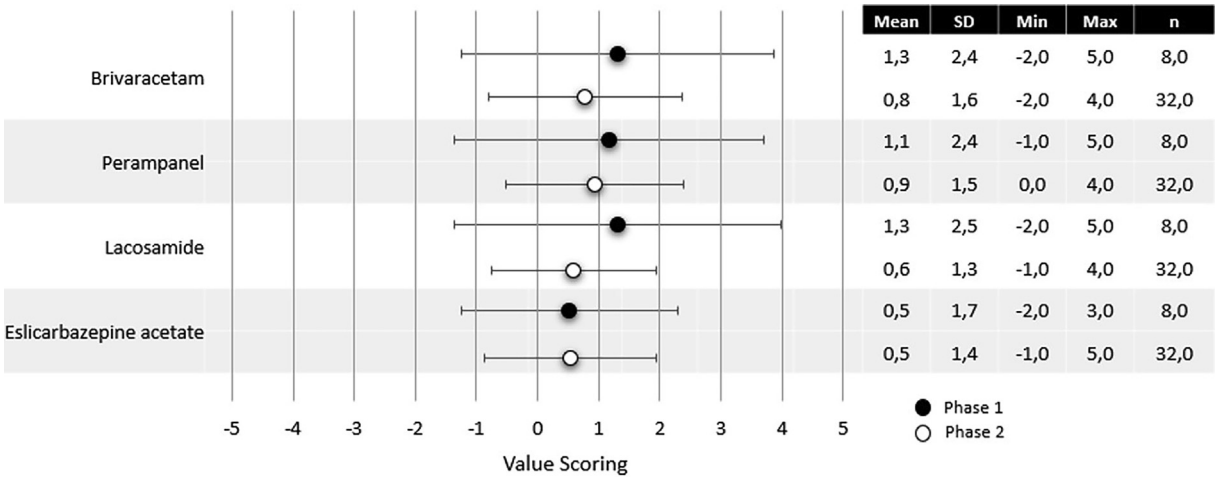


Fig. 2. Comparative efficacy criterion phase 1 and phase 2 value scoring results – cenobamate vs brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate.



	Mean	SD	Min	Max	n
Brivaracetam	-2,1	0,6	-3,0	-1,0	8,0
	-0,6	1,4	-3,0	4,0	32,0
Perampanel	-0,4	1,4	-3,0	2,0	8,0
	0,2	1,6	-2,0	4,0	32,0
Lacosamide	1,0	2,0	-2,0	5,0	8,0
	0,1	1,4	-3,0	4,0	32,0
Eslicarbazepine acetate	-0,5	2,2	-3,0	4,0	8,0
	-0,1	1,3	-2,0	4,0	32,0

Fig. 3. Comparative safety criterion phase 1 and phase 2 value scoring results – cenobamate vs brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate.



	Mean	SD	Min	Max	n
Brivaracetam	1,3	2,4	-2,0	5,0	8,0
	0,8	1,6	-2,0	4,0	32,0
Perampanel	1,1	2,4	-1,0	5,0	8,0
	0,9	1,5	0,0	4,0	32,0
Lacosamide	1,3	2,5	-2,0	5,0	8,0
	0,6	1,3	-1,0	4,0	32,0
Eslicarbazepine acetate	0,5	1,7	-2,0	3,0	8,0
	0,5	1,4	-1,0	5,0	32,0

Fig. 4. Comparative PROs criterion phase 1 and phase 2 value scoring results – cenobamate vs brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate.

that DRE has a high social impact, with great limitations on the patient's independence, added to the stigma and discrimination associated with this condition.

3.1.2. Size of affected population

Overall, DRE is considered to affect a significant number of patients (phase 1: 4.1 ± 1.0; phase 2: 3.2 ± 1.2) (Fig. 1). However, there was a divergence of scores and opinions among profiles (Supp. Fig. 1). Clinicians and patient representatives justified their scores based on their perception that DRE has a high prevalence similar to other neurological diseases such as multiple sclerosis, and that it is currently under-diagnosed. In contrast, evaluators did not consider it to be as prevalent as other chronic diseases such as diabetes or asthma.

3.1.3. Unmet needs

Participants considered that DRE is associated with many and relevant unmet needs with high consensus across stakeholders' profiles (phase 1: 4.3 ± 0.5; phase 2: 4.4 ± 0.7) (Fig. 1), mainly with regard to the lack of more effective treatments to achieve the ultimate goal of treatment, seizure freedom. Explanations also highlighted the delay in diagnosis and instauration of early treatment due to limited access to some diagnostic tests (video-EEG) and specialized units, and the inequity in the management and treatment of DRE patients across different Spanish regions.

3.1.4. Type of therapeutic benefit

The therapeutic benefit of cenobamate is considered relevant (phase 1: 3.4 ± 1.2; phase 2: 3.4 ± 0.8) (Fig. 1). The experts provided the following rationale for their high scores: 1) cenobamate is the first and only ASM approved for the treatment of FOS in adult patients with DRE; 2) it is associated with high responder rates and seizure freedom rates not observed with existing ASMs; 3) its efficacy is independent of the number of previously failed ASMs with a 20% seizure-free rate achieved after failure of at least two ASMs; 4) cenobamate showed high retention rates of 80% in the first year and 60% at 6 years; 5) treatment with cenobamate greatly reduces concomitant ASMs, which results in lower drug burden and optimization of treatment tolerability. However, there was a greater dispersion of scores among profiles in phase 1 (Supp. Fig. 1) as the evaluators assigned lower scores by stating that the type of benefit of cenobamate is limited to symptomatic, thus not modifying the course of disease. Additionally, they pointed out the uncertainty regarding long-term efficacy. On the other hand, patient representatives assigned higher scores, mainly due to the proportion of patients achieving seizure control with treatment with cenobamate.

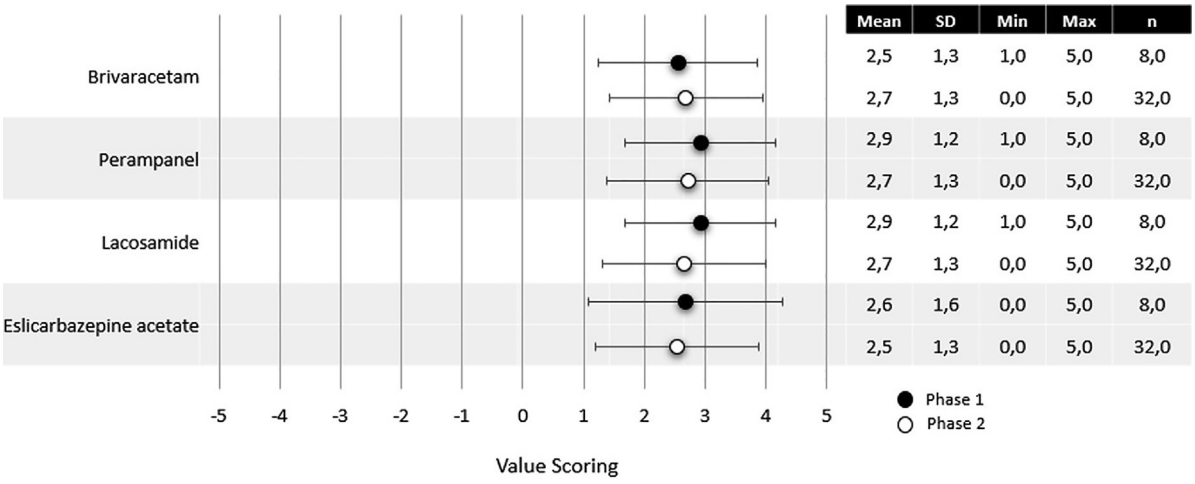


Fig. 5. Comparative other medical costs criterion value scoring results – cenobamate vs brivaracetam, perampanel, Lacosamide, and eslicarbazepine acetate: phase 1 and phase 2.

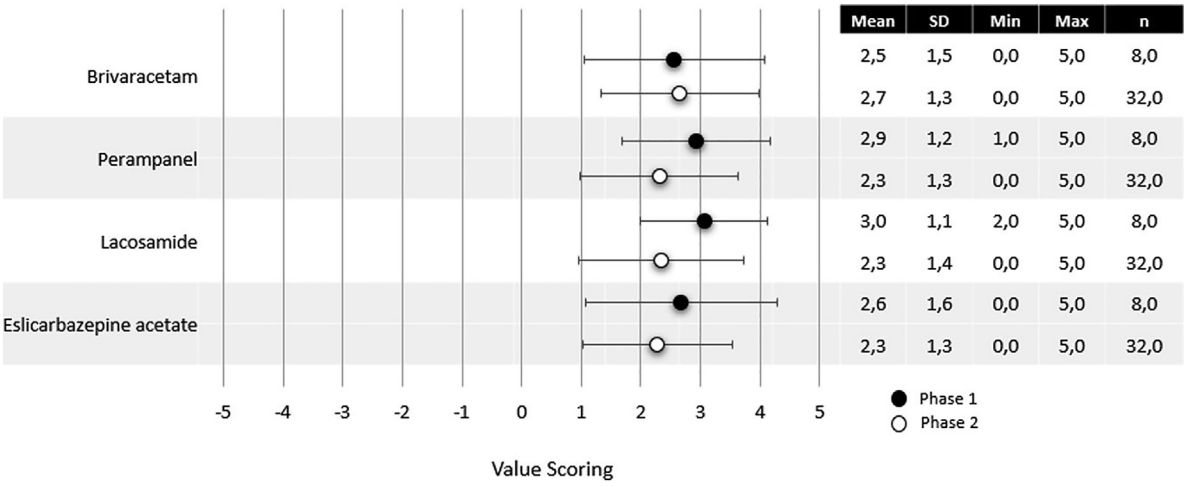


Fig. 6. Comparative indirect costs criterion value scoring results – cenobamate vs brivaracetam, perampanel, Lacosamide, and eslicarbazepine acetate: phase 1 and phase 2.

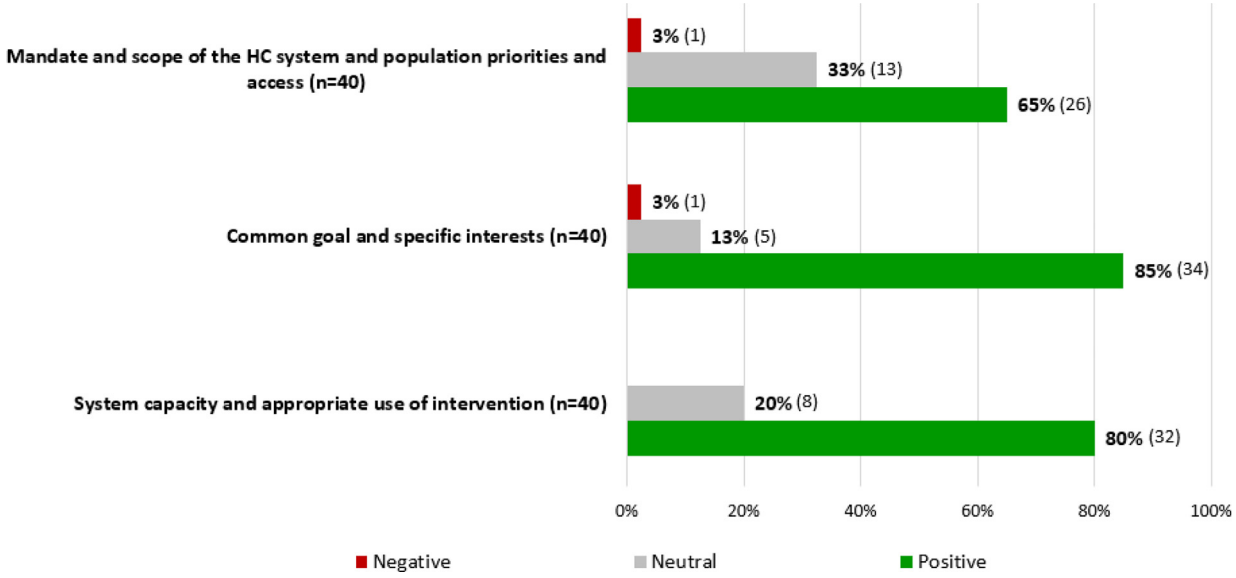


Fig. 7. Qualitative (contextual) criteria value scoring results.

3.1.5. Quality of evidence

Regulatory approval of cenobamate is considered to be supported by high-quality evidence (phase 1: 3.1 ± 1.1; phase 2: 3.9 ± 0.9) (Fig. 1) derived from a robust clinical development program, including clinical endpoints relevant to the targeted indication and with strong study results. Participants considered the pivotal phase II study C017 [16] to be well designed in accordance with EMA's "Guideline on Clinical Investigations of Medicinal Products in the Treatment of Epileptic Disorders" (2018) [30]. Overall, there was consensus among all participants' profiles, although evaluators tended to score slightly lower given the lack of an active comparator in its pivotal study (Supp. Fig. 1).

3.1.6. Experts' consensus/clinical practice guidelines

Overall, experts considered the clinical development of cenobamate to be aligned with clinical practice guidelines (CPG) (phase 1: 3.4 ± 0.7; phase 2: 3.9 ± 1.2). CPG on epilepsy are available at national (SEN) [12]) and regional (Catalan Society of Neurology (SCN) [31], Andalusian Epilepsy Society (SADE) [32], Valencian Neurological Society (SVN) [33]) levels in Spain, which are not specific to DRE, but include recommendations on the management and treatment for this condition. Participants from phase 2 highly positively valued the inclusion of cenobamate in the last update of SEN's CPG published in 2022 as the only effective treatment for DRE, which was not available at the time of conducting phase 1.

3.2. Comparative criteria

3.2.1. Comparative efficacy/effectiveness

Overall, cenobamate is considered by participants to have significantly higher efficacy compared to all third-generation ASMs: brivaracetam (phase 1: 2.9 ± 1.0; phase 2: 2.9 ± 1.1), perampanel (phase 1: 3.8 ± 1.2; phase 2: 3.3 ± 1.1), lacosamide (phase 1: 3.5 ± 1.1; phase 2: 3.0 ± 1.1), and eslicarbazepine acetate (phase 1: 3.4 ± 1.7; phase 2: 3.2 ± 1.2) (Fig. 2) based on data derived from pivotal clinical trials compared to placebo and indirect treatment comparisons (ITC) [28]. The high scores for efficacy, in favor of cenobamate reported by experts, are based on the highest responder rate and seizure freedom rates achieved in clinical trials.

However, this criterion presents a slight dispersion in scores due to differences in perceptions by different profiles (Supp. Fig. 2). Patient representatives from phase 1 valued seizure freedom rate achieved by cenobamate very positively. Additionally, clinicians highlighted the strength of these results as its clinical trial included a more refractory patient group (93.1%) [16] (patients who have failed at least 2 previous ASMs) than in the brivaracetam (75.7%) [34], lacosamide (84.4%) [35], and eslicarbazepine acetate (74.2%) [36] studies and similar to the perampanel clinical trials (100%) [37]. On the other hand, evaluators considered the long titration phase of cenobamate (12 weeks) to be a limitation as it was linked to a potential delay in achieving seizure control. Furthermore, the lack of head-to-head clinical trials between ASMs makes it difficult to compare alternatives.

3.2.2. Comparative safety/tolerability

Overall, the safety profile of cenobamate is considered similar to that of third-generation ASMs, but there was a wide dispersion of scores among participants (Fig. 3).

When comparing cenobamate vs brivaracetam, the results of the statistical analysis showed significant differences between the scores of both study phases. The safety profile of cenobamate was considered by phase 1 participants to be inferior to brivaracetam (-2.1 ± 0.6) based on the higher rates of severe adverse events (AEs), serious AEs, and AEs that led to discontinuation reported in clinical trials. Overall, phase 2 participants scored higher for this criterion than their phase 1 counterparts considering cenobamate to be only slightly less safe than brivaracetam (-0.6 ± 1.4). In this regard, participants justified their scores stating that despite the higher percentage of AEs reported in the cenobamate study, the type of AEs (central nervous system-related AEs) are manageable and transient and without an impact in long-term retention rate data [29]. Therefore, phase 2 participants did not consider that there were any significant differences between the safety profile of the two ASMs [28].

When compared with perampanel, cenobamate's safety profile was considered similar across stakeholder profiles in both phases (phase 1: −0.4 ± 1.4; phase 2: 0.2 ± 1.6) (Suppl. Fig. 3) although physicians raised concerns about the safety profile of perampanel in relation to its association with behavioral disorders (e.g., irritability, aggression).

The safety profile of cenobamate was considered to be slightly superior or similar to lacosamide both in phase 1 (1.0 ± 2.0) and phase 2 (0.1 ± 1.4), respectively. However, a high dispersion in opinions was observed due to differences in perceptions across profiles in phase 1 (Suppl. Fig. 3). Clinicians considered that lacosamide is better tolerated than cenobamate in clinical practice. However, evaluators considered both drugs to have a similar profile based on data reported from clinical trials. Patient representatives scored higher than the rest of participants since they positively valued the frequency of administration of cenobamate (once a day) vs lacosamide's (twice a day), so potential AEs associated with cenobamate (e.g., somnolence, dizziness) could be reduced by taking it before bedtime.

Finally, compared to eslicarbazepine acetate, cenobamate was considered similar by participants from both phases (phase 1: −0.5 ± 2.2; phase 2: −0.1 ± 1.3). There was a wide dispersion in scores among participants with no major differences between profiles, but overall, they perceived both ASMs to have a comparable safety profile, although numerically higher AEs were reported in the cenobamate clinical trial.

3.2.3. Comparative patient reported outcomes (PROs)

Cenobamate was perceived as a drug capable of providing value in terms of patient's QoL compared to third-generation ASMs: brivaracetam (phase 1: 1.3 ± 2.4; phase 2: 0.8 ± 1.6), perampanel (phase 1: 1.1 ± 2.4; phase 2: 0.9 ± 1.5), lacosamide (phase 1: 1.3 ± 2.5; phase 2: 0.6 ± 1.3) and eslicarbazepine acetate (phase 1: 0.5 ± 1.7; phase 2: 0.5 ± 1.4) (Fig. 4), although a high dispersion in opinions between stakeholder profiles was observed in phase 1 (Supp. Fig. 4).

Patient representatives valued the greater rates of seizure reduction and seizure freedom achieved with cenobamate considering it as a positive impact on patients' QoL. They also emphasized that the impact of treatment-related AEs on QoL should be taken into account. None of the ASMs demonstrated to have a clinically significant improvement in the QOLIE-31-P (the patient-weighted quality of life in epilepsy-31) score likely due to the short evaluation period in clinical trials (12 weeks). This was one of the main limitations reported by evaluators in the assessment of this criterion. Besides, physicians stated that QoL significantly improved only when patients experienced a greater reduction in seizure frequency of at least 75% sustained for at least one year [38,39]. In this sense, with 45.3% of patients achieving 75% response rate [16], they expect cenobamate to improve patients' QoL to a greater extent than third-generation alternatives.

3.2.4. Comparative other medical costs

Experts scored cenobamate positively for the "comparative other medical costs" reflecting their perception of the economic benefits obtained, derived from its superior efficacy, due to savings on healthcare resources resulting from better outcomes derived from treatment with cenobamate compared to brivaracetam

(phase 1: 2.5 ± 1.3; phase 2: 2.7 ± 1.3), perampanel (phase 1: 2.9 ± 1.2; phase 2: 2.7 ± 1.3), lacosamide (phase 1: 2.9 ± 1.2; phase 2: 2.7 ± 1.3), and eslicarbazepine acetate (phase 1: 2.6 ± 1.6; phase 2: 2.5 ± 1.3) (Fig. 5). Overall, participants considered that the proven high efficacy of cenobamate could be translated into a lower use of healthcare resources such as visits to specialists, accident & emergency services, and hospitalizations.

Some phase 1 participants noted that these potential savings had not been quantified representing the main limitation of the assessment of this criterion. New evidence such as the economic evaluation of cenobamate [20] was available at the time of conducting phase 2, which led to increased scores by evaluators (Supp. Fig. 5). However, some participants claimed for the need of long-term real-life data confirming results before assigning a higher score.

3.2.5. Comparative indirect costs

Cenobamate is perceived as a therapeutic option that can produce savings in "non-medical costs" compared to brivaracetam (phase 1: 2.5 ± 1.5; phase 2: 2.7 ± 1.3), perampanel (phase 1: 2.9 ± 1.2; phase 2: 2.3 ± 1.3), lacosamide (phase 1: 3.0 ± 1.1; phase 2: 2.3 ± 1.4), and eslicarbazepine acetate (phase 1: 2.6 ± 1.6; phase 2: 2.3 ± 1.3) (Fig. 6). Cenobamate's greater efficacy in seizure control and seizure freedom may contribute to maintaining patients' autonomy, increasing caregivers' productivity, and reduce out-of-pocket related expenses. However, there is a slight dispersion in the range of scores (Supp. Fig. 6), as in particular evaluators assigned lower scores due to the lack of real clinical practice data, which prevents confirmation of actual savings that could be expected with cenobamate treatment compared to third-generation alternatives and hence higher scores.

3.3. Contextual criteria

3.3.1. Mandate and scope of the Healthcare system and population priorities and access

The introduction of a new treatment indicated for DRE patients, such as cenobamate, into the Spanish Healthcare System was considered to be fully aligned with health priorities in this patient population by most participants (65%, n = 26/40), contributing to the achievement of objectives and health outcomes reflected in national and regional strategies and plans. A 33% (n = 13) of stakeholders considered that the introduction of a new treatment would have a neutral alignment due to the lack of specific regional plans for epilepsy, with the exception of the Valencian Community [40]. One participant (3%) assigned a negative alignment since the lack of coordination among Spanish regions hinders the management and access to proper treatment of patients with DRE.

3.3.2. Common goal and specific interests

Most participants (85%, n = 34/40) agreed that the availability of cenobamate within the Spanish Health System would be completely aligned with the objectives and specific interests of stakeholders such as scientific societies and patient associations. Five participants (13%) considered the alignment to be neutral since they perceived that DRE is not a priority within the Chronicity Working Group of the Spanish Society of Hospital pharmacists. One participant (3%) considered that the availability of a new treatment would not be aligned unless it demonstrated efficacy in reducing mortality risk.

3.3.3. System capacity and appropriate use of intervention

Most participants (80%, n = 32/40) considered cenobamate to represent a new therapeutic option for patients with DRE that can be perfectly introduced and used within the Spanish NHS. Moreover, in Spain, there are nine reference centers for refractory epilepsy that work to provide adequate care for these patients, so these participants considered that their introduction would not require additional organizational or training resources. On the other hand, eight participants (20%) considered that due to its requirement for slow titration, treatment with cenobamate may require special training to ensure adequate use.

4. Discussion

The relative value contribution of cenobamate to the treatment of FOS in adult patients with DRE in comparison with the third-generation ASMs was assessed through reflective MCDA by a panel of stakeholders involved in the management of epilepsy and decision-making in Spain. Value scoring allowed holistic value determination of cenobamate, including the specific context of its appraisal in Spain.

Spain's National Health System (NHS) is based on the principles of universality, free access, equity, and fairness of financing. The health system remains almost universal, covering 99.7% of the population and it is funded by social security contributions from working residents with the seventeen autonomous regional governments allocating their own health budget.

Throughout Spain, there are public hospitals, private non-profit hospitals, and private for- profit hospitals. Public hospitals and private hospitals are financed by the seventeen autonomous regions. Medical treatment and general care costs at a public hospital are free for anyone with a Spanish health card.

The study included participation of physicians, evaluators, and patient representatives from five different regions and a total of 31 different hospitals, contributing to collect insights from a broad range of perspectives and different contexts. The majority of study participants, clinicians, hospital pharmacists, and evaluators work in public hospitals with the only exception of a neurologist from a private hospital. No differences in responses between this private sector participant and the rest of public sector participants were identified.

A multidisciplinary approach is key when optimizing the management and treatment of patients with epilepsy. However, at present, the involvement of patient representatives in evaluation and decision-making processes in Spain is limited to providing comments to the national therapeutic positioning reports [41] in which the relative value contribution of a new treatment is stated. However, they do not participate in pricing and reimbursement or formulary introduction decision-making processes taking place at national, regional and hospital levels. Therefore, in order to adequately reflect the current situation in Spain, patients' representatives were excluded from phase 2. In addition, the number of phase 2 participants, corresponding to eight per region, represents the current sample of stakeholders involved in drug evaluation committees at regional level and its composition included evaluators from both healthcare levels (primary and hospital care) involved in the management of patients with epilepsy.

The study was conducted in two separate phases over time, allowing for replication of the study when more published evidence and clinical experience became available. In this way, it was possible to assess whether the perceived value contribution of cenobamate by stakeholders during phase 1 was confirmed or changed on the basis of the new evidence, while also gaining greater robustness of the results with a larger sample of participants. Additionally, the availability of more evidence allows for informed decision-making. When analyzing the scores by profile, it is observed how the differences between clinical and evaluator participants slightly decreased from phase 1 to phase 2, leading to an approximation in their scores.

Findings stated that DRE is perceived as a severe disease with high unmet needs and associated with high morbidity and mortality. There is a great need to improve the early diagnosis of DRE, allowing for the timely instauration of optimal treatment as early as possible, as a way of achieving desired outcomes. In addition, more effective treatments are needed to effectively control seizures positively impacting on DRE comorbidities and thereby improving patients' and caregiver's QoL [6].

When compared to the third-generation ASMs, cenobamate is perceived as bringing important improvements in terms of efficacy based on data reported in its pivotal clinical trial [16], and later confirmed by recently published long-term evidence [42]. Additionally, the improved efficacy of cenobamate compared to third-generation ASMs is supported by ITCs, which reported that cenobamate is ranked best for efficacy [28,43]. However, the lack of direct comparative studies between ASMs was reported as a limitation among evaluators in both phases. Some experts stated that the development of head-to-head clinical trials in epilepsy represents a great challenge since the choice of ASMs are always individualized by patient profile and, hence, patients entering a clinical trial present great heterogeneity of concomitant treatments introducing potential bias in study outcomes [44,45].

Overall, in terms of safety, cenobamate was perceived to have a similar profile compared to alternatives. However, the results of the statistical analysis showed significant differences in scores between phases when comparing the safety profile of cenobamate with brivaracetam. Phase 1 participants rated the safety of cenobamate negatively (mean score −2.1) based on data derived from its pivotal clinical trial [16]. Cenobamate study had a duration of 18 weeks with a 6-week rapid titration and weekly dose escalation [16], while the titration scheme stated in its Summary of Product Characteristics (SmPC) is 21 weeks with a gradual slower titration scheme (every 2 weeks) [46]. Therefore, fewer AEs can be expected in clinical practice than during its clinical development program. In fact, most of the AEs of mild or moderate severity occurred during the titration phase and resolved over time [47]. Additionally, an ITC available at the time of phase 2 reported that no significant differences were observed between ASMs in the proportion of patients experiencing at least one TEAE or in the proportion of patients experiencing at least one TEAE leading to treatment discontinuation [28]. In this sense, phase 2 participants rated this criterion similar to brivaracetam (mean score −0.6) with a slight trend in favor of brivaracetam due to the absence of titration which avoids a longer drug monitoring.

Regarding PROs, the study reflects that cenobamate is perceived as a new treatment capable of improving patients' QoL. Despite the limited availability of data on QoL in these patients, study participants considered that this criterion is often interpreted as an indirect indicator of patient satisfaction with achieved outcomes, representing the balance between long-term efficacy and safety. This would be in line with the high retention rates of cenobamate reported at 80% in the first year and 60% at 6 years [29].

It is noteworthy that the introduction of cenobamate allows for a reduction in the number of concomitant ASMs [48], which could not only benefit both the safety and tolerability profile for the patient but also represent savings in terms of pharmacological costs.

The pharmacological cost criterion was not assessed because, at the moment of the study, cenobamate was undergoing the Pricing & Reimbursement (P&R) process in Spain. On the other hand, cenobamate is considered to save on direct and indirect costs compared to alternatives since its proven high efficacy could translate into a lower long-term use of healthcare resources, and lower productivity loss of the patient and the caregiver, as reflected in a recent publication on the cost-effectiveness analysis of cenobamate [20].

The reflective component of the MCDA methodology used in this study allowed to understand and discuss the rationale behind experts' scores for each value criterion, and to understand the perspectives of different stakeholder profiles contributing to collegiate decision-making.

Reflective MCDA methodology has been recently used in different Spanish studies to help assess value across different medical conditions and therapeutic areas as well as being used as a tool to facilitate evaluation and decision making by Health Technology Agencies and pharmacotherapeutic committees in Spain [49–53]. It is therefore understandable that MCDA methodology is becoming increasingly popular to support healthcare decision-making, particularly in complex cases [54–56].

One limitation typically highlighted in these types of studies is the relatively small number of participants usually included (average 8–12) [8,54]. In an attempt to overcome this limitation, this study included a significant number of participants across a diverse set of stakeholders' profiles, while trying to achieve a balanced geographical representation, accounting for a total of 40 participants from five different Spanish regions.

However, the present study is not exempt from some limitations. The number of stakeholders participating in phase 1 was reduced compared to that in phase 2 which could have introduced some potential bias. To overcome this limitation and to increase result robustness, a statistical analysis of stakeholders' scoring results from both phases was performed. In addition, the higher rate of dispersion in scores reported in phase 1 than in phase 2 may be due to the reduced number of participants, as well as the involvement of the patient representatives' profile in phase 1 as opposed to those in phase 2.

5. Conclusion

To our knowledge, this is the first study to apply MCDA methodology to determine the value contribution of a treatment option for FOS in patients with DRE in Spain. The findings of this study suggest that a robust, representative and multidisciplinary sample of stakeholders in Spain perceived cenobamate as a value-added option for the treatment of FOS in patients with DRE, considered as a severe condition associated with important unmet needs, mainly with regards to the lack of more effective treatments that achieve seizure control.

The application of reflective MCDA methodology not only allows understanding the value perception of a new treatment in a holistic way taking into account a broad spectrum of value attributes and relative to available treatment alternatives, but also support informed decision-making on the selection of the most appropriate therapy for these patients.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M. Falip has received honoraria for advisory boards/consultancy and speaking fees from Angelini, BIAL, ESAI, Esteve, GW Pharmaceuticals/Jazz Pharmaceuticals, UCB Pharma/Zogenix; J. López has participated in advisory boards and industry-sponsored symposia by Angelini, BIAL, Cyberonics, ESAI, Esteve, GSK, Jazz Pharmaceuticals, Pfizer, UCB Pharma; I. Rey Gómez-Serranillos has received fees for his participation in the study from Angelini; V. Merino-Bohórquez has received fees for his participation in the

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Appendix A. Supplementary data

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