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Number needed to treat and associated cost analysis of cenobamate versus third-generation anti-seizure medications for the treatment of focal-onset seizures in patients with drug-resistant epilepsy in Spain

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ABSTRACT

Introduction: Epilepsy is a serious neurological disease, ranking high in the top causes of disability. The main goal of its treatment is to achieve seizure freedom without intolerable adverse effects. However, approximately 40% of patients suffer from Drug-Resistant Epilepsy (DRE) despite the availability of the latest options called third-generation Anti-Seizure Medications(ASMs). Cenobamate is the first ASM approved in Spain for the adjunctive treatment of Focal-Onset Seizures (FOS) in adult patients with DRE. The introduction of a new drug increases the number of therapeutic options available, making it important to compare it with existing alternatives in terms of clinical benefit and efficiency.

Purpose: This study aimed to compare the clinical benefit, in terms of the Number Needed to Treat (NNT), and the efficiency, in terms of Cost per NNT (CNT), associated with cenobamate versus third-generation ASMs used in Spain for the adjunctive treatment of FOS in patients with DRE.

Methods: The Number Needed to Treat data was calculated based on the ≥50% responder rate and seizure freedom endpoints (defined as the percentage of patients achieving 50% and 100% reduction in seizure frequency, respectively), obtained from pivotal clinical trials performed with cenobamate, brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate. The NNT was established as the inverse of the treatment responder rate minus the placebo responder rate and was calculated based on the minimum, mid-range Daily Defined Dose (DDD), and maximum doses studied in the pivotal clinical trials of each ASM. CNT was calculated by multiplying the annual treatment cost by NNT values for each treatment option.

Results: In terms of NNT, cenobamate was the ASM associated with the lowest values at all doses for both ≥50% responder rate and seizure freedom compared with the alternatives. In terms of CNT, for ≥50% responder rate, cenobamate was the ASM associated with the lowest CNT values at DDD and lacosamide and eslicarbazepine acetate at the minimum and maximum dose, respectively. For seizure freedom, cenobamate was associated with the lowest CNT value at DDD and the maximum dose and lacosamide at the minimum dose.

Conclusions: Cenobamate could represent the most effective ASM in all doses studied compared to the third-generation ASMs and the most efficient option at DDD for both ≥50% responder rate and seizure freedom. This study could represent an important contribution towards informed decision-making regarding the selection of the most appropriate therapy for FOS in adult patients with DRE from a clinical and economical perspective in Spain.

Abbreviations: NNT, Number Needed to Treat; CNT, Cost per NNT; FOS, Focal-onset Seizures; DRE, Drug-resistant Epilepsy; ASM, Anti-seizures Medications; DDD, Daily Defined Dose.

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1. Introduction

Epilepsy is one of the most common chronic neurological disorders affecting around 50 million people worldwide [1,2], which corresponds to approximately 200,000 adult patients in Spain [3]. It is characterized by recurrent spontaneous seizures which can be classified as focal or generalized. Focal-Onset Seizures (FOS) are the most common type in the adult population, accounting for more than 60% of patients with epilepsy [4].

Conventional treatment for epilepsy is based on the long-term administration of oral Anti-Seizure medications (ASMs) [5] to achieve seizure freedom without causing side effects. However, approximately 40% of patients, particularly those with FOS, continue to experience seizures despite treatment with at least two ASMs [6], suffering Drug-Resistant Epilepsy (DRE) according to The International League Against Epilepsy (ILAE) [7].

The most recent ASMs approved for FOS in the last decade, the so-called "third-generation ASMs", brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate, although not specifically indicated for DRE, have included patients refractory to previous therapies in their clinical development programs and currently represent the most commonly used options [8]. Third-generation ASMs are considered to be better tolerated and have less drug-drug interaction, being the most recommended for some comorbidities. However, despite their introduction, the probability of achieving seizure freedom has not been substantially modified compared to previous years, remaining at approximately 4% [6,9].

Cenobamate is the first ASM approved (June 2021) and commercialized (September 2022) in Spain [10] 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 [11].

The introduction of a new ASM represents an increase in the number of therapeutic options for the treatment of epilepsy, making it important to compare the new drugs with existing alternatives to be able to determine their relative clinical benefit while contributing to the sustainability of healthcare systems. Considering that healthcare financial resources are limited, the determination of aspects such as efficiency, cost-effectiveness, and return of investment linked, represent much-needed aspects for an adequate decision-making process [12].

The calculations of the Number Needed to Treat (NNT) and the Cost Needed to Treat (CNT), represent simple ways to assess these aspects [13,14]. The NNT is the number of patients that must receive treatment to achieve one additional study endpoint and it has been previously used to determine the relative clinical benefit of several ASMs in the treatment of epilepsy [15–17]. In Spain, NNT analysis is currently used in the assessment of new drugs by evaluation organizations at both regional and hospital levels, which recommend its use as a measure of relative efficiency for new drugs [18–21]. Likewise, CNT has also previously been used to determine the efficiency of drugs for the treatment of other chronic diseases in Spain [22].

The main objective of this study was to determine the clinical benefit, in terms of NNT, and the efficiency, in terms of CNT, associated with cenobamate and third-generation ASMs used in Spain for the adjunctive treatment of FOS in patients with DRE.

2. Methods

2.1. Clinical data and comparators

Efficacy data from published Randomized Controlled Trials (RCTs) (Supplementary Table S1) was used to compute NNT and CNT for cenobamate and third-generation ASMs for the treatment of FOS in patients with DRE in Spain.

Since there is no other ASM authorized in Spain with the same indication as cenobamate, the most commonly prescribed ASMs as third-line adjunctive treatments were chosen as comparators for this analysis. This represents the same treatment line expected for cenobamate according to its Summary of Product Characteristics (SmPC) [11]. The most recent ASMs approved in the last decade, the so-called "third-generation ASMs" (brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate) represent approximately 70% of prescriptions in this line of treatment for patients with DRE in Spain [25], so they were included in this analysis.

Randomized controlled trials selected for this analysis were the pivotal clinical trials considered by the European Medicines Agency (EMA) as part of the marketing authorization approval of each of the selected alternatives (Table 1) [23–26]). Data were derived from an integrated analysis of pooled data from pivotal clinical studies for all ASMs except for cenobamate, which has only one pivotal study. The C013 study of cenobamate was not considered pivotal by EMA, since its 6-week maintenance period was not considered sufficient to demonstrate long-lasting efficacy [27].

In the case of brivaracetam, the N01252 [28] and N01253 [29] pivotal studies included approximately 20% of subjects using concomitant levetiracetam (LEV), while the N01358 study [30] did not include subjects receiving LEV at study entry. The results of the first two studies showed a potential influence of LEV on the global benefit of brivaracetam. Furthermore, the brivaracetam Spanish Therapeutic Positioning Report (TPR) did not recommend the combination of both ASMs [31]. Hence, data included in the current analysis did come from the data pool E1 [32] which combined the three pivotal studies, excluding those patients from the N01252 and N01253 studies who received concomitant levetiracetam.

2.2. Study outcomes

A threshold of 50% or greater reduction in seizure frequency from baseline is often described as a clinically meaningful improvement for a patient with DRE experiencing a high baseline seizure burden. This threshold is used by European regulatory authorities as a primary efficacy endpoint for evaluating new ASMs [27]. Marked improvement in quality-of-life for patients and their caregivers, as well as potential improvement in other non-seizure outcomes such as cognition and behavior, is attained by achieving complete seizure freedom (100% reduction in seizure frequency), considered as the ultimate goal of treatment [38,39].

Hence, the ≥50% responder rate (defined as the percentage of patients achieving ≥50% reduction in seizure frequency) and seizure freedom (defined as the percentage of patients achieving 100% reduction in seizure frequency) were selected as outcomes of interest, defined as the percentage of patients achieving ≥50% and 100% reduction in seizure frequency during the maintenance phase, respectively [27].

Table 1
Pivotal studies for each ASM included in the analysis and source of data.

ASM	Pivotal studies	Reference	
Cenobamate	C017	Krauss GL *et al* 2020	[33]
Brivaracetam	N01252, N01253, N01358	Ben-Menachem E *et al* 2016	[32]
Perampanel	304, 305, 306	Steinhoff BJ *et al* 2013	[34]
Lacosamide	SP667, SP754, SP755	Sake J *et al* 2010	[35]
Eslicarbazepine Acetate	301, 302, 303	Gil-Nagel A *et al* 2013	[36]

For each outcome, NNT was calculated according to the doses studied in clinical trials, differentiating between minimum, mid-range, and maximum doses. The doses corresponding to each drug are shown in Table 2. The mid-range dose of all ASMs, except for lacosamide, corresponds to their individually defined daily dose (DDD) according to their SmPCs [11,23,24,26]. The DDD of lacosamide is 300 mg [44], although it was not studied in pivotal clinical trials [25].

2.3. Costs

Drug costs used in the study corresponded to the ex-factory price for each pharmaceutical presentation after applying the compulsory 7,5% discount for each drug (except for eslicarbazepine acetate and lacosamide, for which the deduction is not applicable [46]) in accordance with Spanish legislation (RDL 8/2010) [47]. Prices were obtained from the Bot Plus database [48] and as published by the General Council of Official Spanish Pharmacists Associations (CGCOF) (Table 3).

The obtained pharmacological costs were multiplied by the number of required daily doses by a patient as indicated in the SmPC of each ASM [11,23–26], adjusted by 52 weeks to calculate the annual cost during the maintenance phase. Costs were calculated according to a minimum, mid-range (DDD), and maximum dose in each case (Table 4).

2.4. NNT and CNT analysis

The method used for calculating NNTs was based on basic methodological recommendations published in the literature [49–51]. In RCTs with a binary endpoint and a defined period of time during which all patients are followed, the NNT is estimated based on the cumulative incidence of the outcome per number of patients, being calculated by inverting absolute risk reduction (ARR) between two treatment options. The ARR is the absolute difference in the rates of events between the incidence of events in the control group and treatment group. The calculation was computed according to the following formula [51] using a public and validated tool developed by the Spanish Society of Primary Care Physicians (SEMERGEN) [27]:

$$NNT = \frac{1}{\pi_1 - \pi_0} = \frac{1}{ARR}$$

π_0: risk control group; π_1: risk in treatment group.

NNT values range from 1 to infinity. The ideal value is 1 since this indicates that every patient treated achieves the predefined clinical benefit. After that, the higher the NNT, the less effective the intervention.

CNT values were calculated by multiplying the annual cost of each therapy according to each of the doses used by its NNT for both outcomes: the ≥50% responder rate and seizure freedom (100% responder rate). CNT estimates were calculated as:

CNT = Annual Pharmacological cost x NNT

3. Results

3.1. NNT

The NNT obtained indicates differences in efficacy in terms of ≥50% responder rate across the ASMs under study. Fig. 1 shows the NNT to achieve an additional ≥50% responder rate with each alternative relative to the placebo.

Considering the results obtained at mid-range dose (DDD), NNTs ranged between 3 and 7. Cenobamate 200 mg (DDD) was associated with the lowest NNT (3), followed by brivaracetam 100 mg (DDD), and lacosamide 400 mg with an NNT value of 5. Eslicarbazepine acetate 800 mg (DDD) was associated with the highest NNT (7).

At the maximum dose, NNTs ranged between 3 and 6. Cenobamate 400 mg (DDD) was associated with the lowest NNT (3) value and brivaracetam 200 mg and perampanel 12 mg with the highest NNT (6).

When considering the minimum dose studied in clinical trials, NNTs ranged between 7 and 71. Cenobamate 100 mg and brivaracetam 50 mg were associated with the lowest NNT (7) and eslicarbazepine acetate 400 mg with the highest value (71), being 10 times higher than the former.

Bigger differences were found when calculating NNT according to seizure freedom (100% reduction in seizure frequency).

Fig. 2 shows the NNT needed to achieve an additional patient with seizure freedom with each alternative relative to the placebo.

Considering the results obtained at mid-range dose, NNTs ranged between 10 and 60. Cenobamate 200 mg (DDD) was associated with the lowest NNT (10), followed by brivaracetam 100 mg with an NNT value of 22. The ASM with the largest difference in NNT compared to cenobamate was eslicarbazepine acetate with a value six times higher (60).

At the maximum dose, NNT values ranged between 5 and 33. Cenobamate 400 mg was associated with the lowest NNT (5) compared to third-generation alternatives, which were linked with NNT values of 19, 25, 28, and 33, corresponding to eslicarbazepine acetate, lacosamide, brivaracetam and perampanel, respectively.

When considering the minimum dose studied in clinical trials, NNT values ranged between 27 and 103. Perampanel 4 mg was the ASM with the lowest NNT (27). Cenobamate 100 mg (34) was associated with an NNT of 34, followed by brivaracetam and lacosamide with values of 50 and 51, respectively. Eslicarbazepine acetate was associated with the highest NNT value (103).

3.2. CNT

Table 5 and Fig. 3 show the annual CNT to achieve an additional ≥50% responder rate with each treatment dose relative to placebo.

For the mid-range dose (DDD), the most efficient ASM was cenobamate, followed by lacosamide 400 mg, eslicarbazepine acetate, brivaracetam, and perampanel, with CNT values ranging from 4,403 € (cenobamate) to 6,753 € (perampanel).

The ranking of CNT when calculated based on maximum dose was eslicarbazepine acetate followed by cenobamate, lacosamide,

Table 2
Daily doses of each ASM studied in their pivotal clinical trials.

ASM		Dosage (mg/day)		
		Minimum dose	Mid-range dose (DDD)	Maximum dose
Cenobamate	[33]	100	200	400
Brivaracetam	[32]	50	100	200
Perampanel	[34]	4	8	12
Lacosamide	[35]	200	400	600
Eslicarbazepine acetate	[36]	400	800	1,200

Table 3
Ex-factory Price for ASMs, showing number of Tablets per Pack, Dose per Tablet, and Ex-factory price after compulsory discount.

ASM	Tablets per Pack	Dose per Tablet	Ex-factory Price	Ex-factory price after applying RDL 8/2010 discount
Cenobamate	28	100 mg	95.15 €	88.01 €
Cenobamate	28	200 mg	112.00 €	103.60 €
Brivaracetam	56	25 mg	112.00 €	103.60 €
Brivaracetam	56	50 mg	112.00 €	103.60 €
Brivaracetam	56	100 mg	112.00 €	103.60 €
Perampanel	28	4 mg	95.76 €	88.58 €
Perampanel	28	8 mg	105.84 €	97.90 €
Perampanel	28	12 mg	115.92 €	107.23 €
Lacosamide	56	100 mg	45.08 €	45.08 €*
Lacosamide	56	200 mg	90.19 €	90.19 €*
Eslicarbazepine acetate	60	200 mg	32.76 €	32.76 €*
Eslicarbazepine acetate	30	800 mg	65.52 €	65.52 €*

* The 7.5% deduction established in RDL 8/2010 for lacosamide and eslicarbazepine acetate is eliminated, according to the Nomenclature of the Ministry of Health for the month of October 2022 and October 2021, respectively.

Table 4
Annual Pharmacological Cost per patient according to dosage of each ASM.

ASM	Annual Cost (€)		
	Minimum dose	Mid-range dose (DDD)	Maximum dose
Cenobamate	1,147.32 €	1,350.50 €	2,701.00 €
Brivaracetam	1,350.50 €	1,350.50 €	1,350.50 €
Perampanel	1,154.68 €	1,276.22 €	1,397.77 €
Lacosamide	587.65 €	1,175.69 €	1,763.54 €
Eslicarbazepine acetate	398.58 €	797.16 €	1,195.74 €

perampanel, and brivaracetam, with CNT values ranging from 5,979 € (eslicarbazepine acetate) to 8,103 € (brivaracetam).

When calculating CNT according to the minimum dose of each ASM, the efficiency ranking, from most to least efficient, was lacosamide, followed by cenobamate, brivaracetam, perampanel, and eslicarbazepine acetate, with CNT values ranging from 5,289 € (lacosamide) to 28,299 € (eslicarbazepine acetate).

Table 6 and Fig. 4 show the CNT to achieve seizure freedom with each treatment dose relative to the placebo.

Considering the results obtained at mid-range dose, the most efficient ASM was cenobamate, followed by brivaracetam, eslicarbazepine acetate, lacosamide, and perampanel, with CNT values ranging from 13,181 € (cenobamate) to 49,773 € (perampanel).

Ranking according to maximum dose was cenobamate, followed by eslicarbazepine acetate, brivaracetam, lacosamide, and perampanel, with CNT values ranging from 13,451 € (cenobamate) to 46,126 € (perampanel).

On the other hand, for the minimum dose of each ASM, the efficiency ranking, from most to least efficient, was lacosamide, perampanel, cenobamate, eslicarbazepine acetate, and brivaracetam, with CNT values ranging from 29,970 € (lacosamide) to 51,319 € (brivaracetam).

4. Discussion

The increasing number of treatment options and the level of expenditure associated with the treatment of patients with DRE underline the need for economic evaluations in this field [52]. Different strategies may be used in economic analyses, such as cost-effectiveness, cost-utility, cost-minimization, cost-benefit, and cost-consequence, calculated based on the number needed to treat (NNT) [53]. Despite the importance of economic analyses, the complexity of some models may impose comprehension difficulties on clinicians and non-economist policy-makers [54].

The NNT is now extensively used in RCTs to provide an additional and user-friendly measure of the impact of active treatment on a given disease outcome and represents a useful tool for clinical and economic decision-making [13,55]. Research has shown that

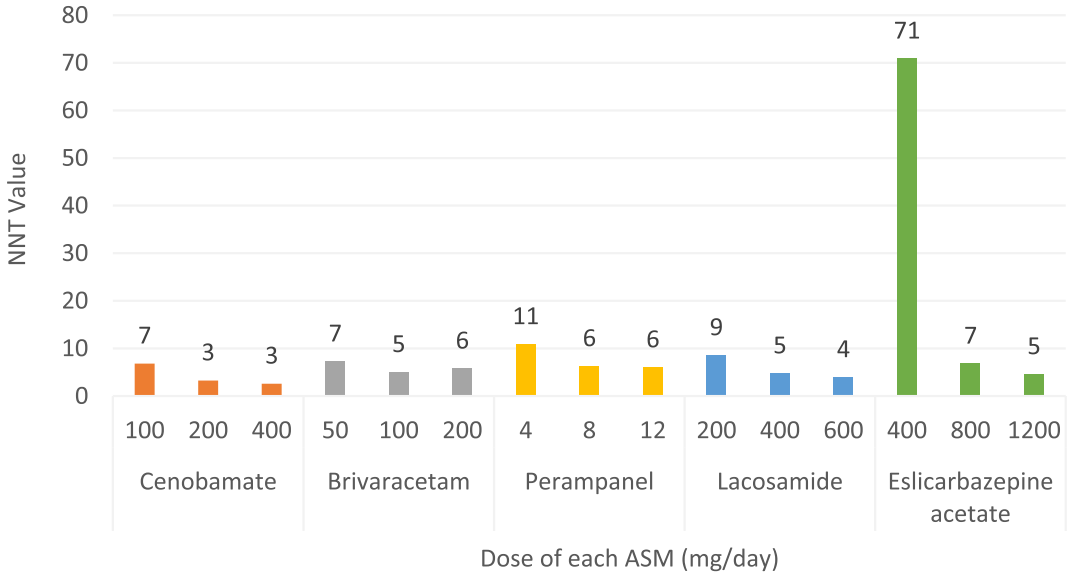

Fig. 1. NNT for ≥50% Responder Rate for each ASM dose.

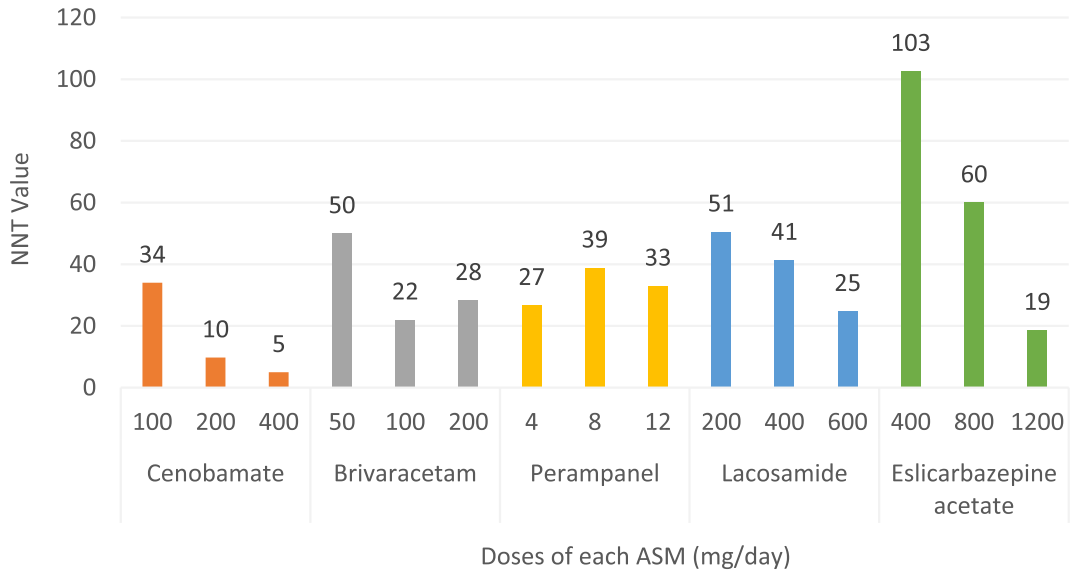

Fig. 2. NNT for Seizure freedom for each ASM dose.

Table 5
Annual CNT Values for ≥50% Responder Rate.

	Minimum dose	Mid-range dose (DDD)	Maximum dose
Cenobamate	7,802 €	4,403 €	6,969 €
Brivaracetam	9,454 €	6,753 €	8,103 €
Perampanel	12,701 €	7,657 €	6,989 €
Lacosamide	5,289 €	5,878 €	7,054 €
Eslicarbazepine acetate	28,299 €	5,580 €	5,979 €

the method of reporting trial results can have a significant influence on treatment decisions made by clinicians, policymakers, evaluators, and patients [56,57].

Number needed to treat methodology is endorsed by scientific societies and commonly used to assess the efficiency of new drugs by evaluation organizations in Spain. The Evaluation of Novelties, Standardization, and Research in Drug Selection Group (GENESIS) of the Spanish Society of Hospital Pharmacy (SEFH) considers the NNT to be a simple and reliable tool that allows an intuitive and comparable interpretation of the practical interpretation of outcomes measures from a study. This group recommends in their guidelines the use of NNT as a measure to present efficacy results indicating that the Incremental Cost-Effectiveness Ratio (ICER) and the estimate of budgetary impact should be calculated based on NNT results [18].

Furthermore, regional evaluation bodies such as the Medicinal Products Advisory Council for Primary and Community Care and Specialized Care (CAMAPCE) of Catalonia included NNT analysis in the evaluations of both brivaracetam and perampanel for the 50% responder rate outcome in the treatment of patients with epilepsy. However, the results are not comparable with our study, as the NNTs included in these evaluations were displayed for each pivotal study individually and not as a pooled analysis of pivotal clinical studies [19,20].

Lower NNT values indicate the need to treat a lower number of patients to obtain an additional benefit. Likewise, lower CNT values mean lower costs associated with obtaining such additional benefits. Hence, putting these results into context, this study suggests that cenobamate (at DDD) represents the most effective and efficient treatment option compared to the third-generation ASMs

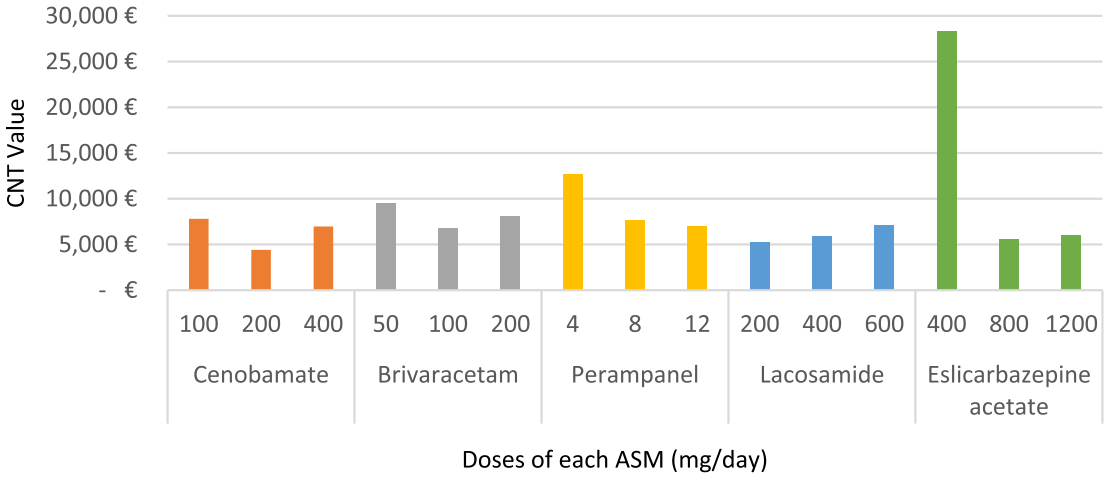

Fig. 3. Annual CNT for ≥50% Responder Rate.

Table 6
Annual CNT Values for Seizure Freedom.

	Minimum dose	Mid-range dose (DDD)	Maximum dose
Cenobamate	39,009 €	13,181 €	13,451 €
Brivaracetam	51,319 €	21,608 €	37,814 €
Perampanel	31,176 €	49,773 €	46,126 €
Lacosamide	29,970 €	48,203 €	44,088 €
Eslicarbazepine acetate	41,054 €	47,830 €	22,719 €

alternatives available in Spain to achieve both ≥50% responder rate and seizure freedom outcomes, based on outcomes of clinical trials.

Considering the ≥50% responder rate, the most efficient options at the minimum and maximum dose would be lacosamide and eslicarbazepine acetate, respectively. Although these ASMs have been demonstrated to be less effective than cenobamate in terms of NNT at both doses, they are subject to reference pricing [46]) and hence the annual costs of lacosamide and eslicarbazepine acetate are 1.7 and 2.3 times lower than cenobamate's.

When considering the seizure freedom outcome, cenobamate represents the most efficient option both at DDD and at a maximum dose with important differences in comparison to the alternatives. At DDD, cenobamate was associated with NNT values 2 to 6 times lower than the third-generation ASMs, while at the maximum dose the difference was 4 to 6 times lower. On the other hand, at the minimum dose, lacosamide represents the most efficient option.

The differential increased clinical benefit of cenobamate versus third-generation ASMs reported in this study is aligned with recent publications.

A network meta-analysis (NMA) performed across third-generation ASMs for the treatment of FOS in patients with DRE has demonstrated that cenobamate is ranked best for efficacy compared to brivaracetam, perampanel, lacosamide, and eslicarbazepine acetate [58].

Previous analysis has also evaluated the relationship between the clinical and economic benefits of cenobamate compared to third-generation ASMs, through a cost-utility analysis. The study showed that cenobamate produces incremental clinical benefit over third-generation ASMs and represents a cost-effective option for DRE patients even at a price 59% above its ex-factory price [59].

To our knowledge, this is the first study that determines the clinical benefit and the determination of the efficiency of cenobamate and third-generation ASMs available in Spain through NNT and CNT analysis.

4.1. Limitations

There are assumptions and limitations associated with this analysis.

Unlike cost-effectiveness analysis, CNT is not a useful measure for establishing a threshold to inform decisions on how much should reasonably be invested in achieving a health outcome.

No assessment is made of potential cost offsets-for example, the cost of hospital admission or surgical or other procedures either avoided or induced by the treatment. Nor are the harmful effects of the drug and the cost associated with managing this effect considered. Finally, there is no attempt to put "value" on a particular outcome such as the number of "years of life gained" or to determine through a cost-utility analysis the cost per "quality adjusted life-years" (QALYs) gained [59]. Despite these limitations, for the clinician and payer appraising and considering the implementation of a new therapy, CNT provides rapid insight as to the drug cost at a population level for the given effectiveness as determined by the RCT.

The studies for the different comparators included in this analysis differed in their duration and patient population (number of seizures per month, number of prior or concomitant ASM). Additionally, due to the short duration of the pivotal RCTs (12–13 weeks), NNT values were extrapolated to one year of treatment to perform the annual CNT calculation. Hence, clinicians and other investigators should be aware that the calculation and interpretation of NNTs depend on specific study characteristics.

This analysis does not provide an indirect comparison of cenobamate and third-generation ASMs currently used in the treatment of FOS in adult patients with DRE in Spain. Results are reported descriptively without statistical analysis to determine whether differences in NNT values are significantly different between the alternatives. However, some authors have suggested that differences in NNTs as low as 0.5 are sufficient to distinguish clinically meaningful differences between treatments [60,61].

On the other hand, the variables used for this analysis are the responder rate and seizure freedom, which represent the number of patients achieving 50% and 100% reduction in seizure frequency, respectively. Therefore, the results obtained are not derived from a median of analyzed data, so no associated Confidence Intervals are available in the clinical trials to quantify in this analysis.

5. Conclusion

Our results suggest that, at DDD, cenobamate could represent the most effective and efficient treatment when considering both ≥50% responder rate and seizure freedom outcomes compared to

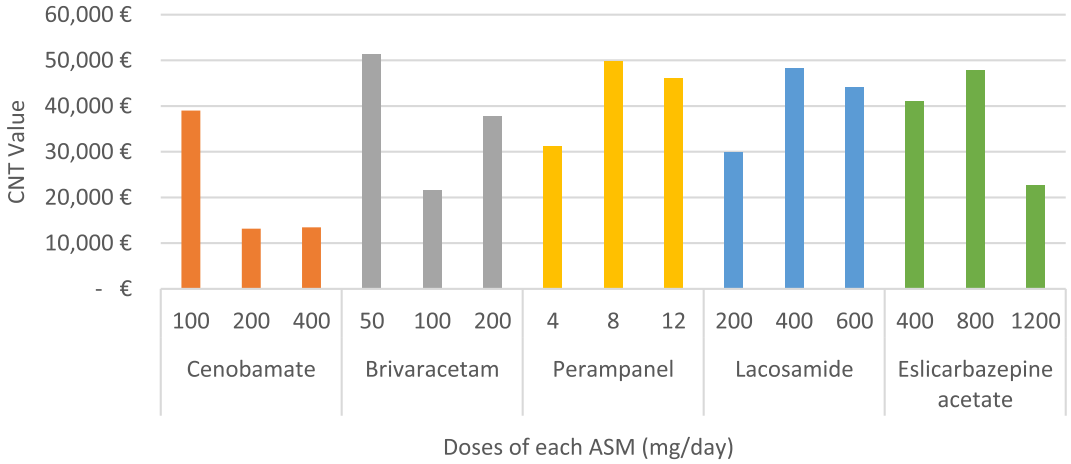

Fig. 4. Annual CNT for Seizure freedom.

alternatives currently used in Spain for the treatment of FOS in patients with DRE.

This analysis is the first to provide information on the clinical and economic impact of cenobamate compared to third-generation ASMs based on NNT and CNT in Spain. Findings from this analysis could represent an important contribution towards informed decision-making regarding the selection of the most appropriate (both from a clinical and economical point of view) therapy for patients while contributing to the sustainability of the healthcare system.

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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: VV has participated in advisory boards and industry-sponsored symposia by Angelini, Bial, Eisai Inc, Jazz Pharmaceuticals, Novartis, Takeda, UCB Pharma, and Zogenix. JMS has received research grants or honoraria as speaker or participant in advisory boards from Angelini, BIAL, Eisai Inc, Esteve, Ferrer, Jazz Pharmaceuticals, GW Pharmaceuticals, Sanofi, UCB Pharma, and Zogenix for participation in advisory boards or pharmaceutical industry-sponsored symposia. MT has participated in DRE clinical trials with different ASMs development and reports receiving consulting fees from Angelini, Bial, Eisai Inc, GSK, GW Pharmaceuticals, and UCB Pharma. MAC has received honoraria for participating in advisory boards/consultancy from Angelini, Amgen, Janssen, Pfizer, Roche, Novartis, Alexion, Lilly, Bayer, AstraZeneca, Galápagos, BMS, Almirall, UCB, MSD, Abbvie, Mylan, Sanofi, Teva. AN has received honoraria for presentations and advisory boards from Angelini, GSK, Bristol, MSD, Pfizer, and ASTRA and a congresses registration fee from Janssen. JS, PPD, and EAB are employees of Angelini. SS and AG are employees of Omakase Consulting S.L. which receive funding from Angelini to develop this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.109054.

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