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ORIGINAL ARTICLE

Effectiveness and safety of early add-on therapy with brivaracetam in patients with poorly controlled focal seizures in routine clinical practice: BRIV-add study

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Abstract

Objective: To evaluate the effectiveness and safety of brivaracetam (BRV) as an add-on therapy in patients with focal onset seizures who did not achieve seizure freedom with antiseizure medication (ASM) monotherapy in routine clinical practice.

Methods: This was a retrospective, observational, multicenter study conducted across 17 neurology centers in Spain. We evaluated adult patients with focal onset epilepsy who had inadequate seizure control after at least 3 months of ASM monotherapy and were treated with dual therapy, combining BRV with their previous ASM, with the intention of maintaining this treatment for at least 6 months. Data were collected from medical records on seizure frequency, ASM doses, and adverse events (AEs), taking into account the end of this 6-month period of dual therapy. The primary efficacy outcomes were the proportion of patients achieving ≥50% reduction in seizure frequency and those achieving seizure freedom. Safety outcomes included the incidence of treatment-related AEs.

Results: A total of 195 patients (mean age: 43.2 years; 52.3% male; mean disease duration: 11.5 years) were included in the study. The main location of epilepsy was identified (53.8%) as the frontal lobe (27.7%). The mean number of seizures during the last 3 months of ASM monotherapy was 12.1 (SD 39.5), which decreased to 6.4 (SD 21.2) after 6 months of BRV add-on therapy. A ≥ 50% reduction in seizure frequency was achieved by 90.8% of patients, while 49.7% reached seizure freedom. The most common AEs were related to the central nervous system,

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reported by 22.1% of patients, with a treatment discontinuation rate due to AEs of 12.8%.

Significance: BRV as an add-on therapy is effective in reducing seizure frequency and is well-tolerated in patients with focal onset seizures. This study supports the use of BRV as an add-on option in patients who do not achieve adequate seizure control with ASM monotherapy.

Plain Language Summary: This study evaluated how effective and safe brivaracetam (BRV) is when added to another medication for patients with focal onset seizures. The results showed that adding BRV helped many patients reduce the number of seizures, and some patients stopped having seizures completely. Side effects were generally mild.

KEYWORDS
antiseizure medication, brivaracetam, combination, drug therapy, epilepsy, focal onset seizures, seizures

1 | INTRODUCTION

Epilepsy affects an estimated 50 million people worldwide, making it one of the most common neurological disorders in the world.[1] Its prevalence in Europe is 0.7% of the population, affecting about six million people.[2] In Spain, the estimated lifetime prevalence, adjusted for age and sex per 1000 people, is 14.87 (95% CI: 9.8–21.9).[3] Focal onset seizures are the most common type of seizure, accounting for 61% of all epilepsy cases.[4] About 50–60% of patients achieve lasting seizure freedom with their first antiseizure medication (ASM). However, for patients with focal seizures who fail to respond to the initial treatment, approximately 20–30% will not achieve satisfactory seizure remission even after switching or adding other treatment options.[4] If the first ASM is not effective in controlling seizures, combining two or more ASMs is often used to exploit the synergistic effects of polytherapy.[2,5]

Brivaracetam (BRV) is a novel ASM that has emerged as an option for the treatment of epilepsy.[6–8] BRV exhibits a high affinity for the synaptic vesicle protein 2A (SV2A), binding with 15 to 30 times greater affinity and selectivity than levetiracetam.[7] It has been extensively studied as an add-on therapy in several randomized controlled trials (RCTs) for patients with drug-resistant focal onset seizures.[9–12] These trials have demonstrated that BRV doses of 50–200 mg/day lead to clinically significant reductions in seizure frequency and achieving seizure freedom, with a low incidence of adverse events (AEs) and low rates of BRV discontinuation due to AEs.[9–11] In Europe, the European Medicines Agency (EMA) has approved BRV as an adjunctive therapy in the treatment of partial-onset seizures with or without secondary generalization in adults, adolescents, and children from 2 years of age with epilepsy.[13] In the United States, the Food and Drug Administration has indicated BRV for treating partial onset seizures in patients 1 month and older, either as monotherapy or adjunctive therapy.[14]

In routine practice, when ASM + BRV combinations fulfill the pharmacological criteria necessary for a rational polytherapy regimen (different mechanism of action, distinct adverse effect profile, no drug interactions, etc.), healthcare providers may consider them suitable.[8,15–17] However, the effectiveness and safety of the various possible ASM + BRV combinations are not yet well established under naturalistic conditions in Spain.

Key points

- BRV as an add-on therapy significantly reduces seizure frequency in patients with focal onset seizures.
- Approximately 49.7% of patients achieved seizure freedom with BRV in dual therapy.
- Dual therapy with BRV demonstrated a favorable safety profile with manageable adverse events.
- BRV is particularly effective in controlling focal to bilateral tonic–clonic seizures.
- The study supports the use of BRV as a first add-on therapy in patients with inadequate seizure control.

The present study aims to evaluate, in the context of routine clinical practice, the effectiveness and safety of combining an ASM with BRV as the first add-on therapy in patients indicated for combination with BRV after not achieving seizure freedom with ASM monotherapy. We also aim to know whether demographic or clinical factors can help predict which patients may benefit from the combination therapy.

2 | METHODS

This is an observational study based on the retrospective clinical assessment of a group of patients with epilepsy treated with dual therapy using any ASM + BRV under routine practice conditions and according to the professional clinical judgment of the investigators (specialists from the Neurology Departments of the participating centers). Effectiveness and efficacy were compared in the last 3 months of monotherapy versus the first 6 months of dual therapy with ASM + BRV. All clinical information in the study was collected by gathering information already available in the medical records of patients who were eligible and consented to collaborate. The study had a naturalistic orientation that did not modify the usual clinical practice of the participating services or professionals.

2.1 | Scope of study

Participation was requested from neurology specialists in hospital centers in Spain with a particular interest and dedication to epilepsy (working in specific units or general neurology consultations) and who were familiar with the therapeutic option of interest in this study (ASM + BRV dual therapy). The review of medical records was performed between December 2021 and January 2023, corresponding to the period of data collection for the study.

2.2 | Study population

The investigating physicians reviewed the medical records of patients they had personally treated. Inclusion criteria were: (1) patients ≥18 years old at the time of their first focal seizure diagnosis, with no prior history of epilepsy or seizures, under follow-up for treatment in the neurology services of the participating hospitals; (2) active and adequately updated clinical history; (3) eligible patients' records showed that they had undergone, before the date of data collection, a period of at least 3 months of treatment with monotherapy with their first ASM, following the estimated achievement of therapeutic plasma levels. The addition of BRV as the first add-on was made due to the persistence of seizures despite monotherapy, indicating inadequate seizure control based on the treating physician's clinical judgment. The switch was followed by another period of dual therapy (ASM + BRV) with a planned follow-up of at least 6 months. During this time, it was not necessary to maintain the same treatment regimen. (4) The investigating specialist is responsible for regular clinical follow-up of the patient's ASM and has authorized access to the patient's clinical history for patient monitoring.

The exclusion criteria were as follows: (1) patients under 18 years of age; (2) patients without an active and adequately updated medical record in the service; (3) patients who are not under the responsibility of the specialist investigator for the follow-up of ASM or who do not have authorized access to their medical records; (4) patients who have been recruited for any clinical trial related to their epilepsy episodes in the past year.

2.3 | Method of patient recruitment and selection

Each investigator reviewed the service files for potential candidate patients based on their clinical and therapeutic profiles. In centers with a large eligible population, investigators selected up to 20 cases that met the criteria, starting from the most recent and working backward chronologically. For centers without a centralized registry, investigators identified eligible patients during routine clinical reviews until either 20 patients were found or all potential candidates had been screened. All eligible patients were included in chronological order without preferential selection based on treatment outcomes or other subjective criteria to minimize selection bias.

2.4 | Variables

Clinical and demographic variables collected included seizure type, epilepsy etiology (idiopathic/genetic, structural, or cryptogenic), age at onset, disease duration, and results of diagnostic tests (MRI and EEG). The location of epilepsy was determined by integrating clinical data, including seizure semiology, interictal and ictal EEG findings, and neuroimaging results (primarily MRI). This integrated approach was used to classify the epilepsy location for each patient. To assess treatment effectiveness and safety, variables were collected during the last 3 months of monotherapy and the first 6 months of dual

therapy. In each period, the proportion of seizure-free patients and patients with ≥50% seizure reduction at the end of the study (≥50% responder patient), monthly seizures, and total seizures were collected. A ≥50% responder patient was defined as a patient in whom a reduction of at least 50% in the number of monthly seizures was achieved in the 6 months following the addition of BRV compared to the baseline situation (monthly seizures in the previous 3 months of initial ASM monotherapy). The proportion of patients who discontinued treatment and the cause of discontinuation were collected from the dual therapy period, including ineffectiveness (defined as the interruption of BRV or the initiation of another ASM simultaneously), adverse events, clinical improvement, and patient choice. Concerning safety, the AEs in each period were summarized in eight categories (psychiatric, central nervous system, ocular, ear and labyrinth, gastrointestinal, general disorders, trauma, and cardiovascular disorders) or specific to each category. In particular, AEs specific to BRV were analyzed, and it was evaluated whether their frequency corresponded to that indicated in the technical data sheet.[18]

2.5 | Sample size

A sample size of 196 patients was estimated. This sample size would allow estimation of dichotomously categorized outcomes, seizure freedom (vs. persistent seizures), and clinically relevant improvement (vs. insufficient), with an error of less than 7%, for a confidence level of 93%, and assuming the worst-case outcome ($p = q = 0.7$) of a binomial distribution.

2.6 | Statistical analysis

The distribution of relative frequencies (%) of each option is shown for qualitative variables. Quantitative variables were described using the usual measures of centralization and dispersion (mean and standard deviation), using the median and interquartile range in cases of wide or atypical dispersion of the data. Possible differences between monotherapy and dual therapy periods were analyzed using statistical tests appropriate to each case (chi-square, Student's t, analysis of variance [ANOVA], or their non-parametric equivalents). To assess the individual and interaction effects of each factor on the dependent variable, a 2×2 interaction analysis (two-way ANOVA) was conducted. Uni- and multivariate (forward Wald) studies were performed on patients on dual therapy to determine characteristics associated with effectiveness variables (seizure-free patients and patients with ≥50% seizure/month reduction). The multivariate model included variables with a p-value <0.10 in the univariate analysis. Version 29.0 of the SPSS-W integrated package was used.

2.7 | Ethical aspects

This study was conducted following the ethical requirements of the Declaration of Helsinki, Fortaleza revision (Brazil, October 2013) for human subjects research. All data included in the survey were processed anonymously following current legislation on data protection. Patients signed an informed consent, and the project was approved by the Clinical Research Ethics Committee of the Hospital Regional Universitario de Málaga (no. UCB-BRIP-2018-02).

3 | RESULTS

A total of 17 hospitals in seven Spanish Autonomous Communities and 20 investigators participated in the study. Data from 195 patients were included, 50.8% male, with a mean age of 46.4 years (SD 18.4). The mean age of epilepsy debut was 33.9 years (SD 18.4), and the mean time of epilepsy evolution was 13.7 years (SD 14.9). Fifty-two percent had structural epilepsy, and 42.6% had epilepsy of unknown origin. The main locations of epilepsy were the temporal lobe and frontal lobe (53.8% and 27.7% of cases, respectively). The clinical and demographic characteristics of the patients are summarized in Table 1.

3.1 | Clinical-therapeutic information of the initial period in monotherapy

The information on the monotherapy period is summarized in Table 2. The most commonly used ASM in this period was eslicarbazepine acetate (33.3%), lacosamide (20.0%), and lamotrigine (15.9%). The mean number of months under treatment in monotherapy was 40.1 months (SD 35.1). In the last 3 months of this treatment, patients experienced a mean of 12.1 seizures (SD 39.5). 33.3% of the patients experienced AEs attributable to the treatment, mainly affecting the central nervous system (CNS) (Table S1).

3.2 | Clinical-therapeutic information of the treatment period with ASM + brivaracetam

Information on the period of dual therapy with ASM + BRV is summarized in Table 3 and Figure 1. In

TABLE 1 Patient demographic and clinical information.

n	195
Age, mean (SD)	46.4 (18.4)
Sex male, *n* (%)	99 (50.8)
Age of onset of epilepsy, mean (SD)	33.9 (18.4)
Years of evolution, mean (SD)	13.7 (14.9)
Type of seizures, *n* (%)	
Focal	54 (27.7)
Focal to bilateral tonic–clonic	51 (26.2)
Both	90 (46.2)
Type of epilepsy, *n* (%)	
Structural	103 (52.8)
Unknown origin	83 (42.6)
Idiopathic-genetic	9 (4.6)
Location, *n* (%)	
Temporal lobe	105 (53.8)
Frontal lobe	54 (27.7)
Multifocal	10 (5.1)
Occipital	6 (3.0)
Parietal	6 (3.0)
Other	8 (4.1)
Unknown	6 (3.0)
Abnormal magnetic resonance imaging, *n* (%)	107 (54.9)
Electroencephalogram with IED, *n* (%)	145 (74.4)
Etiology, *n* (%)	
Cerebrovascular disease	22 (11.3)
Brain tumor	17 (8.7)
Cranioencephalic trauma	11 (5.6)
Central nervous system infection	10 (5.1)
Mesial sclerosis	5 (2.6)
Alcoholism/toxicants	2 (1.0)
Heterotopia	4 (2.0)
Degenerative disease	2 (1.0)
Non-injury	14 (7.2)
Unknown	67 (31.8)
Other etiologies with ≤3 cases	41 (21.0)
Patients with any somatic comorbidity, *n* (%)	132 (70.0)
Main somatic comorbidities, *n* (%)[a]	
Arterial hypertension	28 (12.6%)
Dyslipemia	15 (6.8)
Hypothyroidism	7 (3.2)
Bronchial asthma	7 (3.2)
Diabetes mellitus	4 (1.8)
Smoking	4 (1.8)
Other comorbidities with ≤3 cases	154 (68.4)
Patients with any psychiatric comorbidity, *n* (%)	80 (43)
Main psychiatric comorbidities, *n* (%)[a]	
Depressive disorder	25 (26.6)
Anxiety disorder	21 (22.3)
Anxious-depressive disorder	9 (9.6)
Behavioral disorder	4 (4.3)
Other comorbidities with ≤3 cases	35 (37.2)

Abbreviations: IED, interictal epileptiform discharges; SD, standard deviation.

[a]Up to three comorbidities could be mentioned.

TABLE 2 Clinical and therapeutic information on the initial treatment period with ASM in monotherapy.

n	195
Initial ASM used in monotherapy, *n* (%)	
Eslicarbacepine acetate	65 (33.3)
Lacosamide	39 (20.0)
Lamotrigine	31 (15.9)
Carbamazepine	19 (9.7)
Oxcarbazepine	15 (7.7)
Valproate	11 (5.6)
Zonisamide	6 (3.1)
Levetiracetam	4 (2.0)
Gabapentin	2 (1.0)
Topiramate	2 (1.0)
Phenytoin	1 (0.5)
Months on treatment with ASM in monotherapy	
Mean (SD)	40.1 (35.1)
Median (IQR)	24 (58)
Number of seizures during the last 3 months of the period on monotherapy	
Mean (SD)	12.1 (39.5)
Median (IQR)	3 (7)
Patients with AEs attributable to the ASM in the last 3 months, *n* (%)	65 (33.3)
AEs attributable to the ASM in the last 3 months, *n* (%)	
Central nervous system disorders	71 (36.4)
General disorders	9 (4.6)
Ocular disorders	9 (4.6)
Gastrointestinal disorders	7 (3.6)
Psychiatric disorders	6 (3.0)
Ear and labyrinth disorders	2 (1.0)
Cardiovascular disorders	1 (0.5)

Abbreviations: AEs, adverse events; ASM, antiseizure medication; IQR, interquartile range; SD, standard deviation.

TABLE 3 Clinical and therapeutic information of the treatment period with AED + brivaracetam.

n	195
Months on treatment with ASM + brivaracetam	
Mean (SD)	22 (18)
Median (IQR)	13 (27)
Treatment interruptions or changes, *n* (%)	44 (22.6)
Cause of discontinuation or change in treatment, *n* (%)	
Adverse events	25 (12.8)
Ineffectiveness	12 (6.2)
Clinical improvement[a]	5 (2.6)
Patient's choice	2 (1.0)
Number of seizures in the first 6 months with ASM + brivaracetam	
Mean (SD)	6.4 (21.2)
Median (IQR)	1 (3)
Patients with AEs attributable to any ASM in the first 6 months, *n* (%)	43 (22.1)
AEs attributable to any ASM in the first 6 months, *n* (%)	
Central nervous system disorders	42 (21.5)
Psychiatric disorders	8 (4.1)
General disorders	5 (2.6)
Gastrointestinal disorders	1 (0.5)
Ear and labyrinth disorders	1 (0.5)

Abbreviations: AEs, adverse events; ASM, antiseizure medication; IQR, interquartile range; SD, standard deviation.

[a]Discontinuation due to improvement refers to situations where patients experience significant reductions in seizures, leading their physicians to stop BRV treatment.

the first 6 months of treatment, patients suffered a total of 6.4 seizures on average (SD 21.2), especially at the beginning of the follow-up period (Figure S1). The mean time on treatment with ASM + BRV was 22 months (SD 18). At the end of the 6-month follow-up period, 77.4% of patients were still on BRV treatment. Treatment with BRV was discontinued in 12.8% of cases due to AEs, in 6.2% due to ineffectiveness (interruption in eight patients and initiation of another ASM in 4), and in 3.6% due to other reasons (improvement in five patients and patients' choice in two cases). A 22.1% experienced an AE attributable to some ASM in this period, most CNS alterations (Table S2). The prevalence of AE's characteristics of BRV coincided with those expected as very frequent (somnolence 12.8% and dizziness 3.5%) or frequent (fatigue 1.5%), although behavioral alterations, which are classified as rare, occurred in four patients (2%) (Table S3).

3.3 | Comparison of effectiveness results

Table 4 summarizes the effectiveness results for the last 3 months of monotherapy with ASM and the first 6 months of dual therapy with ASM + BRV. During the period of dual therapy, 49.7% of patients remained seizure-free. In a univariate study, seizure freedom in the dual therapy group was statistically significantly associated with sex, seizure type, location, and ASM used in monotherapy (Table S4). In a multivariate study, the absence of seizures was statistically significantly associated with focal to bilateral tonic–clonic seizures ($p = 0.009$) and with the location of epilepsy in the temporal lobe ($p = 0.035$).

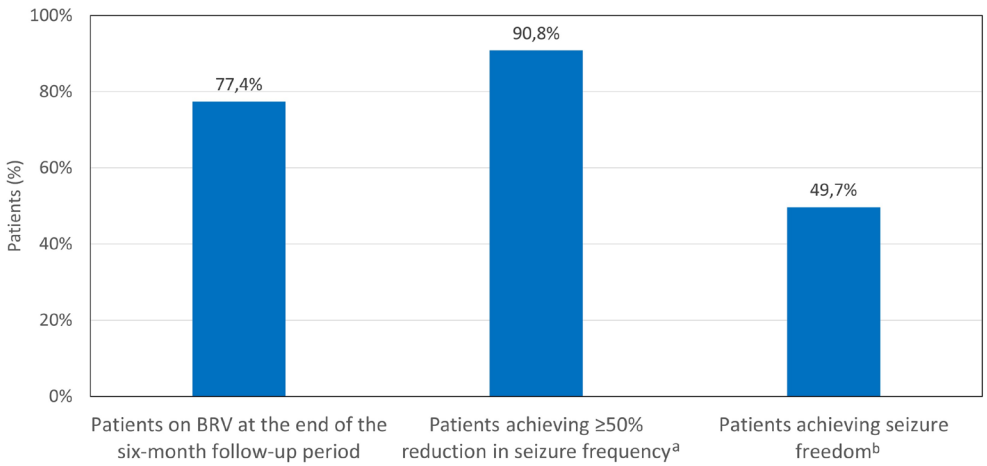

FIGURE 1 Effectiveness outcomes of brivaracetam add-on therapy in patients with focal onset seizures. ASM, antiseizure medication; BRV, brivaracetam; SD, standard deviation. [a]A ≥ 50% responder patient was defined as a patient in whom a reduction of at least 50% in the number of monthly seizures was achieved in the 6 months following the addition of BRV compared to the baseline situation (monthly seizures in the previous 3 months of initial ASM monotherapy). [b]Proportion of seizure-free patients in the 6 months after adding BRV.

TABLE 4 Comparison of effectiveness results between monotherapy with ASM and dual therapy with ASM + brivaracetam.

Effectiveness variable[a]	ASM in monotherapy	ASM + brivaracetam	*p*
Seizure-free patients, *n* (%)	0	97 (49.7)	<0.001
≥50% responder patients, *n* (%)	0	177 (90.8)	<0.001
Number of monthly seizures			
Mean (SD)	4.05 (0.94)	1.07 (0.25)	<0.001
Median (IQR)	1 (2.4)	0.17 (0.5)	<0.001
75th percentile	3	0.5	
90th percentile	7	2.5	
Total seizures			
Mean (SD)	12.1 (2.8)	6.4 (1.5)	<0.001
Median (IQR)	3 (7)	1 (3)	<0.001

Abbreviations: ASM, antiseizure medication; IQR, interquartile range; SD, standard deviation.

[a]Results are shown for the last 3 months of monotherapy with an ASM vs. the first 6 months of dual therapy with ASM + brivaracetam.

At the end of the study, 90.8% of patients on dual therapy were ≥50% responder patients. No significant differences were found between patients with or without ≥50% response with dual therapy and their demographic and clinical characteristics in the uni- or multivariate study.

The number of seizures per month was reduced from 4.05 (SD 0.94) with monotherapy to 1.07 (SD 0.25) with dual therapy ($p < 0.001$). In a univariate analysis, the only factor associated with the reduction in the number of seizures per month between monotherapy and dual therapy was the location of epilepsy in the temporal lobe ($p = 0.01$). Statistical significance was found in the interaction of the following factors: (1) Type of seizure × location of epilepsy ($p < 0.001$). (2) Type of seizure × location of epilepsy × ASM used in initial monotherapy ($p = 0.01$). (3) Type of epilepsy × location of epilepsy × ASM used in initial monotherapy ($p < 0.001$).

Monthly seizure reduction according to the drug in monotherapy is shown in the supplementary material (all drugs and doses are listed in Table S5, and data organized by drug and mechanism of action, regardless of doses, is shown in Table S6). No significant differences were found in the reduction in monthly seizures according to the initial ASM. There was a reduction in mean monthly seizures with all monotherapy treatments except topiramate (only two patients in this group) (Table S6). In four patients, levetiracetam + BRV was used. In two patients, the mean monthly seizures increased from 0.3 to 0.8; in one patient, it changed from one to 0; and in another, from 0.7 to 0.

Considering the total sample over the entire study period, the total number of seizures went from 12.1 (SD 2.8) in 3 months of monotherapy to 6.4 (SD 1.5) in 6 months of dual therapy ($p < 0.001$).

3.4 | Comparison of safety results

The proportion of patients with AEs attributable to treatment was higher in the monotherapy period (65 patients, 33.3%) vs. the dual therapy period (45 patients, 22.1%, $p = 0.012$). The number of AEs per patient considered globally by categories or individually was lower in the dual therapy group (Table 5). The category of AEs related to CNS or ocular disorders was significantly lower in the dual therapy group (Table 5). Details of the differences between the specific AEs are given in Table S7. Regarding specifically the psychiatric AEs, the incidence of depression was 1.5% ($n = 3$) in the ASM monotherapy group and 2.1% ($n = 4$) in the dual therapy group ($p = 1$). Other psychiatric AEs were reported in 1.5% ($n = 3$) of the monotherapy group (all with irritability) and 2.1% ($n = 4$) of the dual therapy group (three patients with irritability and one with behavioral disorders) ($p = 1$).

4 | DISCUSSION

This retrospective analysis carried out in Spain shows the efficacy of BRV as an add-on therapy to an ASM in patients who have not achieved seizure freedom with ASM monotherapy. The results suggest that effectiveness is associated with seizure type and epilepsy location, with patients with focal to bilateral tonic–clonic seizures and those with epilepsy located in the temporal lobe achieving seizure freedom to a greater extent.

Dual therapy was generally well-tolerated, and BRV's safety profile did not change from that described in the datasheet. The treatment discontinuation rate was low due to AEs or lack of efficacy.

TABLE 5 Comparison of adverse events between ASM monotherapy and dual therapy with ASM + brivaracetam.

	ASM in monotherapy	ASM + brivaracetam	*p*
n	195	195	
Patients with AE, *n* (%)	65 (33.3)	43 (22.1)	0.012
General AEs, *n* (%)			
Psychiatric	6 (3.0)	8 (4.1)	0.574
CNS	71 (36.4)	42 (21.5)	0.02
Eye	9 (4.6)	0 (0)	0.04
Ear and labyrinth	2 (1.0)	1 (0.5)	1
Gastrointestinal	7 (3.6)	1 (0.5)	0.068
General disorders	9 (4.6)	5 (2.6)	0.415
Cardiovascular	1 (0.5)	0 (0)	1
General AEs per patient, mean (SD)[a]	0.44 (0.73)	0.25 (0.51)	0.001
Specific AEs per patient, mean (SD)[b]	0.54 (0.93)	0.17 (0.44)	<0.001

Abbreviations: AE, adverse effect; ASM, antiseizure medication; CNS, central nervous system; SD, standard deviation.

[a]General AEs refer to eight categories: psychiatric disorders, central nervous system disorders, eye disorders, ear and labyrinth disorders, gastrointestinal disorders, general disorders, trauma and cardiovascular disorders.

[b]Details of the specific AEs are shown in the Table S7.

The efficacy and tolerability of BRV for the adjunctive treatment of focal seizures in patients ≥16 years of age were established in four Phase III, randomized, multicenter, double-blind, placebo-controlled, multicenter, Phase III trials.[9–12] At doses of 50–200 mg/day of BRV, clinically relevant seizure freedom and seizure frequency reduction were observed, with a low incidence of AEs and low discontinuation rates due to AEs, in a systematic review and meta-analysis of those four Phase III RCTs[9–12] and two other Phase IIb RCTs.[19,20] Participants who received BRV as add-on therapy to other ASMs were significantly more likely to experience a ≥50% reduction in seizure frequency (RR: 1.81, 95% CI: 1.53–2.14) or to achieve seizure freedom (RR: 5.89, 95% CI: 2.30–15.13) than those who received placebo. The incidence of treatment discontinuation for any reason (RR: 1.27, 95% CI: 0.94–1.74), as well as the risk of participants experiencing one or more AEs (RR: 1.08, 95% CI: 1.00–1.17), was not significantly different after treatment with BRV compared with placebo.[6]

Experience with BRV as an add-on therapy to monotherapy in real-life studies is limited, but it has been increasing in recent years.[7,8,15,16,21–24] The largest real-life study to date Villanueva et al.[25] is an aggregate analysis of individual patient records from multiple independent, non-interventional, retrospective studies that used chart review cohorts of patients who initiated BRV in clinical practice.[25] This study summarized real-world data from different countries on specific groups of patients (including patients with varying types of seizure, on monotherapy, and who switched to BRV from other ASMs). It included a total of 1644 patients ≥16 years of age from Spain ($n = 740$), Germany ($n = 488$), Australia ($n = 291$), and the United States ($n = 125$), 92.2% of whom had focal seizures,[25] 92.2% with focal seizures. A seizure reduction ≥50% was achieved in 32.1%, 36.7%, and 36.9% of patients at 3, 6, and 12 months, respectively (analysis of patients with at least one documented seizure at baseline). In the assessment of all patients, seizure freedom rates were 22.4%, 17.9%, and 14.9%, and the proportion of patients maintaining BRV treatment was 89.4%, 79.8%, and 71.1% at 3, 6, and 12 months, respectively.

In our study, the 6-month rates of seizure-free and ≥ 50% responder patients were 49.7% and 90.8%, respectively. These results are better than those found in the aggregate analysis of Villanueva et al. probably because the participants in that study are poorer prognosis patients as 97.3% were using polytherapy with ASM at the time of BRV addition and 84.6% had received two or more previous ASMs. However, the proportion of patients who remain on treatment with BRV at 6 months is similar, 77.4% in our study and 79.8% in the study by Villanueva et al.[25]

A 12-month, prospective, real-world, noninterventional study conducted across nine European countries (EP0077/NCT02687711) assessed the effectiveness and tolerability of adjunctive BRV in patients aged 16 and older with focal onset seizures in routine clinical practice

($n = 544$).[16] In this study, BRV demonstrated significant efficacy as an adjunctive therapy in patients with predominantly refractory focal onset seizures. At the 12-month mark, 57.7% of patients continued BRV treatment, with 60.4% achieving ≥50% seizure reduction since baseline. Notably, 13.8% of patients attained complete seizure freedom since initiating BRV. The study discontinuation rates were 16.4% due to AEs and 12.9% due to lack of efficacy. Interestingly, prior use of levetiracetam did not appear to influence the retention rate of BRV. This study is not directly comparable to ours due to patient complexity and follow-up duration differences. It included more complex patients with a mean of 7.3 lifetime ASMs and a median of 3.7 focal onset seizures per 28 days during the 3-month baseline period. The follow-up was also longer. However, both studies support BRV's usefulness as an adjunctive therapy in focal onset seizures. They provide complementary perspectives on its application in various patient groups.[16]

A multicenter retrospective study (BRIVAFIRST) in Italy assessed the effectiveness and tolerability of adjunctive BRV in a large population of patients (≥16 years of age) with epilepsy in clinical practice.[15] Data were compared for patients treated with add-on BRV after 1–2 (early add-on) and ≥3 (late add-on) prior ASMs. A total of 1029 patients with focal epilepsy were included in the study, of whom 176 (17.1%) received BRV as early add-on treatment. Sustained seizure response (≥50% reduction in seizure frequency) was reached by 60.3% of patients in the early add-on group and 34.3% in the late add-on group ($p < 0.001$). Sustained seizure freedom was achieved by 31.7% of patients in the early add-on group and 10.9% in the late add-on group ($p < 0.001$). During the 1-year study period, 16.5% of patients in the early add-on group and 28.3% in the late add-on group discontinued BRV ($p = 0.001$). Overall, 30.1% of patients reported AEs. The most common AEs included somnolence, nervousness and/or agitation, vertigo, and fatigue. The longer duration of follow-up in BRIVAFIRST (12 months vs. 6 months in our study) prevents direct comparisons with our study. Nevertheless, both studies suggest that early use of BRV as add-on therapy is associated with better outcomes regarding seizure control compared to its later use in treating focal seizures.

Multivariate analyses analyzing the factors associated with greater effectiveness in our study showed that the treatment is more effective in terms of the proportion of seizure-free patients, in patients with temporal lobe epilepsy, and in those with focal to bilateral tonic–clonic seizures. According to pivotal studies and studies in clinical practice, BRV is an effective ASM for generalized onset seizures, both primary and focal to bilateral tonic–clonic (Villanueva et al[25]). Understandably, its addition to ASM with other mechanisms of action improves efficacy in this type of seizure, as shown in our study. However, the interaction analysis results revealed statistically significant associations between several factors, such as type of seizure, location of epilepsy, and the ASM used in initial monotherapy. These interactions suggest that the effectiveness of BRV treatment as an add-on therapy depends on a complex combination of clinical and pharmacological factors.

The population with generalized seizures has a higher risk of falls, morbidity, and mortality compared to the population with other types of seizures.[26] Therefore, it is interesting to highlight the effectiveness of BRV in the population with focal to bilateral tonic–clonic seizures. The effectiveness of BRV in these patients is also high, as shown in the study by Villanueva et al.[25] The results of a post hoc analysis of long-term (up to 11.3 years) pooled data from double-blind Phase III trials of adjunctive BRV and the corresponding open-label, long-term follow-up trials revealed that among patients who completed at least 1 year of adjuvant treatment with BRV, 51.3% were free of focal to bilateral tonic–clonic seizure for ≥1 year during the entire treatment period; approximately 23% were free of these seizures during the first year (from the first day of BRV treatment), and approximately 36% reported no seizures during the second year of BRV treatment.[26]

Regarding the effectiveness and safety of BRV according to previous monotherapy, the number of combinations of BRV at different doses with other drugs was 102, making it difficult to draw conclusions because it involves a small number of patients, in some cases only one. Studies evaluating the efficacy of BRV with specific ASM are scarce.[27,28] In our study, except with topiramate, which was only used in two patients, a reduction in the number of monthly seizures was observed with all combinations and doses of BRV, suggesting its value as an add-on therapy to any monotherapy. However, levetiracetam and BRV were combined in four patients with poor results in two of them. This is not a surprising outcome since they are drugs with a similar mechanism of action, and their combined use is not recommended.

With respect to AEs, our study shows a safety profile of BRV that is compatible with that described in the datasheet. Furthermore, the results suggest that the AE burden is not higher than with monotherapy, and the dropout rate due to AE is low.

Our study has limitations inherent to retrospective studies, such as, for example, clinical history selection bias, underreporting of AEs, or the possible variability of the professionals when collecting data. Some centers had difficulties recruiting the predetermined number of eligible patients, and some did not reach the initial quota. When a larger eligible population was available, each investigator selected the last 20 consecutive cases that met the criteria.

However, the total number of patients meeting the inclusion criteria at each center was not calculated, which prevents knowing what percentage of the eligible population was ultimately included. In addition, data were not collected on the severity of AEs or on time variables, such as seizure-free time, which could be more precise when collected retrospectively. Regarding safety, we observed fewer AEs with dual therapy compared to monotherapy. While this may be due to dose reductions of one or both components of the dual therapy, we acknowledge that data on dose reductions were not collected, which is a limitation of our study. This lack of information prevents us from drawing definitive conclusions about the reasons for the reduced incidence of AEs. Despite all this, the study collects key variables of effectiveness and safety, and it can provide evidence of its usefulness in real life.

5 | CONCLUSION

BRV added to ASM monotherapy in natural clinical practice conditions is effective and safe in patients who fail to achieve seizure freedom in monotherapy. The effectiveness in terms of seizure freedom may be greater in patients with focal to bilateral tonic–clonic seizures and temporal lobe epilepsy. Further studies are needed to determine the effectiveness and safety of specific combinations of BRV with other ASMs, but BRV appears useful in most possible combinations.

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CONFLICT OF INTEREST STATEMENT

Pedro J. Serrano-Castro: Pedro J. Serrano-Castro has been an invited speaker for, and participated in advisory boards organized by Eisai Ltd., Bial, Esteve, UCB-Pharma, Angellini Pharma, Jazz Pharmaceutical, Roche, and Novartis. Fernando Caballero-Martínez: declared no conflicts of interest. Francisco J. Campos-Lucas: declared no conflicts of interest. Daniel Campos-Fernández: declared no conflicts of interest. María José de Aguilar-Amat has been an invited speaker for and participated in advisory boards organized by Eisai Ltd., Bial, Esteve, UCB-Pharma, Angellini Pharma, and Jazz Pharmaceutical. Alberto García: he participado como ponente en reuniones patrocinadas por UCB-Pharma, Eisai Ltd., Bial y Angellini Pharma. Ariadna Gifreuhas received academic support from UCB Pharma, Bial Pharmaceutical, Angelini Pharma, Merck, Bristol-Myers-Squibb, Biogen, Janssen, Novartis, Roche, Neuraxpharm. Irene Santamaría-Rodríguez: declared no conflicts of interest. Juan José Pozahas been an invited speaker for and participated in advisory boards organized by Eisai Ltd., Bial, Esteve, UCB-Pharma, Angellini pharma, Jazz Pharmaceutical, GSK, Pfizer, Sanofi, Novartis, ADAMED, and Alter. Manuel Toledo-Argany has received funding and grants from Eisai Ltd., Bial, Esteve, UCB-Pharma, Angellini pharma, and Jazz Pharmaceutical.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

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

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