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ORIGINAL RESEARCH ARTICLE

Adjunctive Brivaracetam in Focal Epilepsy: Real-World Evidence from the BRIVAracetam add-on First Italian netwoRk STudy (BRIVAFIRST)

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Abstract

Background In randomized controlled trials, add-on brivaracetam (BRV) reduced seizure frequency in patients with drug-resistant focal epilepsy. Studies performed in a naturalistic setting are a useful complement to characterize the drug profile.

Objective This multicentre study assessed the effectiveness and tolerability of adjunctive BRV in a large population of patients with focal epilepsy in the context of real-world clinical practice.

Methods The BRIVAFIRST (BRIVAracetam add-on First Italian netwoRk STudy) was a retrospective, multicentre study including adult patients prescribed adjunctive BRV. Patients with focal epilepsy and 12-month follow-up were considered. Main outcomes included the rates of seizure-freedom, seizure response (≥ 50% reduction in baseline seizure frequency), and treatment discontinuation. The incidence of adverse events (AEs) was also considered. Analyses by levetiracetam (LEV) status and concomitant use of strong enzyme-inducing antiseizure medications (EiASMs) and sodium channel blockers (SCBs) were performed.

Results A total of 1029 patients with a median age of 45 years (33–56) was included. At 12 months, 169 (16.4%) patients were seizure-free and 383 (37.2%) were seizure responders. The rate of seizure freedom was 22.3% in LEV-naive patients, 7.1% in patients with prior LEV use and discontinuation due to insufficient efficacy, and 31.2% in patients with prior LEV use and discontinuation due to AEs ($p < 0.001$); the corresponding values for ≥ 50% seizure frequency reduction were 47.9%, 29.7%, and 42.8% ($p < 0.001$). There were no statistically significant differences in seizure freedom and seizure response rates by use of strong EiASMs. The rates of seizure freedom (20.0% vs. 16.6%; $p = 0.341$) and seizure response (39.7% vs. 26.9%; $p = 0.006$) were higher in patients receiving SCBs than those not receiving SCBs; 265 (25.8%) patients discontinued BRV. AEs were reported by 30.1% of patients, and were less common in patients treated with BRV and concomitant SCBs than those not treated with SCBs (28.9% vs. 39.8%; $p = 0.017$).

Conclusion The BRIVAFIRST provided real-world evidence on the effectiveness of BRV in patients with focal epilepsy irrespective of LEV history and concomitant ASMs, and suggested favourable therapeutic combinations.

1 Introduction

Antiseizure medications (ASMs) play a central role in the treatment of people with epilepsy. Although several medications became available in the last decades, the prevalence of refractory epilepsy remains high and around one-third of patients continue to have incomplete seizure control [1, 2]. Due to ongoing seizures, patients often experience psychological dysfunction, social stigma, reduced educational

The members of the "BRIVAFIRST Group Membership" are listed in Acknowledgement section.

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Key Points

Adjunctive brivaracetam (BRV) improved seizure frequency in patients with focal epilepsy irrespective of levetiracetam history.

Seizure response was higher among patients treated with BRV and concomitant sodium channel blockers (SCBs).

Adverse events were less frequently observed when BRV was concomitantly administered with SCBs than with no SCBs.

and employment opportunities, impaired quality of life, and increased mortality [3]. Therefore, the development of new therapeutic options that are effective and safe is needed.

Brivaracetam (BRV) is a rationally developed compound characterized by high-affinity binding to synaptic vesicle protein 2A (SV2A) and chemical structure similar to levetiracetam (LEV) [4]. BRV is highly lipid-soluble, comparable with benzodiazepines and phenytoin. It is almost completely absorbed after oral administration and enters the brain rapidly by crossing the blood–brain barrier via passive diffusion [5, 6]. BRV is weakly (< 20%) bound to plasma proteins and is rapidly and evenly distributed in most tissues. The pharmacokinetics of BRV are dose-proportional within the range of 10–600 mg. The drug is eliminated primarily by metabolism and by excretion in the urine, and the plasma half-life is approximately 9 h [5, 6]. BRV is primarily metabolized by hydrolysis of the acetamide group to the corresponding carboxylic acid metabolite, and secondarily by hydroxylation on the propyl side chain to form the hydroxy metabolite [5, 6]. The hydrolysis is mediated by hepatic and extrahepatic amidase, and the hydroxylation is mediated primarily by cytochrome P450 (CYP) 2C19. An additional hydroxy acid metabolite is produced by hydrolysis of the amide moiety on the hydroxy metabolite or hydroxylation of the propyl side chain on the carboxylic acid metabolite mainly through CYP2C9. None of the three main metabolites, namely acid, hydroxy, and hydroxy acid, are pharmacologically active [5, 6].

BRV does not interact with most drug-metabolizing enzymes and drug transporters, and is associated with few clinically relevant drug–drug interactions (DDIs) [7]. The effect of BRV on other ASMs has been evaluated in a meta-analysis of five pivotal trials [8]. No clinically relevant changes in plasma concentrations have been observed and no dose adjustment was needed when BRV at doses of up to 200 mg/day was added to common ASMs (carbamazepine, lacosamide, lamotrigine, LEV, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, and zonisamide) [7]. One exception was the dose-dependent increased exposure to carbamazepine-epoxide, the active metabolite of carbamazepine, due to BRV-mediated inhibition of epoxide hydrolase, and the effect size was not influenced by concomitant valproic acid [7]. In a *post hoc* analysis of clinical trials of adjunctive BRV, this inhibition has not been found to have clinically significant effects on safety or efficacy [9]; dose reduction of carbamazepine should however be considered if tolerability issues arise in patients receiving concomitant BRV. In a population pharmacokinetic modelling study of adults with focal seizures who participated in pivotal trials, carbamazepine, phenytoin and phenobarbital/primidone, which have strong enzyme-induction properties on many enzymes, decreased BRV levels by 26%, 21% and 19%, respectively, with no significant influence on clinical response [10]. Dose adjustment and an increase in BRV dose of up to 100% should be considered when it is coadministered with the potent CYP2C19 inducer rifampin [7]. St. John's wort (*Hypericum perforatum*) is also a strong CYP inducer that may decrease BRV levels, and caution is needed when this herbal supplement is added or ended [7]. As BRV did not significantly inhibit or induce CYP3A and had no effects on midazolam metabolism, it would not be expected to interact with the oral anticoagulants apixaban and rivaroxaban [7]. BRV has been shown to modestly inhibit CYP2C19 in studies in human liver microsomes, and the potential increase in plasma levels of drugs primarily metabolized by CYP2C19 (e.g., diazepam, lansoprazole, omeprazole) cannot be excluded [7]. Furthermore, BRV weakly inhibits phenytoin metabolism through CYP2C19 inhibition in in vitro studies, and a pharmacokinetic study in patients with epilepsy demonstrated that BRV administered at the supratherapeutic dose of 400 mg/day increased phenytoin exposure by approximately 20% [11]. There is evidence suggesting that BRV can be safely coadministered with inhibitors of CYP2C8 or CYP2C9, and BRV exposure should not be significantly affected by coadministration with any CYP2C19 inhibitor [7, 12]. Furthermore, in vitro studies demonstrated no significant inhibition of drug transporters [7]. The overall low propensity of DDIs, which may be partly attributed to the presence of multiple elimination pathways and the major elimination route occurring through amidases, for which DDIs have not been reported, may allow the administration of BRV without dose adjustment and avoid potential untoward events [7].

In randomized, placebo-controlled trials, BRV reduced seizure frequency when added to pre-existing ASMs in patients with drug-resistant focal epilepsy [13]. The aim of this study was to assess the effectiveness and tolerability of adjunctive BRV over a 1-year period in a large population of patients with focal epilepsy treated in the context of real-world clinical practice.

2 Methods

2.1 Participants

The BRIVAFIRST (BRIVAracetam add-on First Italian networK STudy) was a retrospective study conducted across 62 Italian centres. Adult (age ≥ 16 years) patients attending participating centres who were prescribed BRV (March 2018–March 2020) and were receiving stable treatment with one or more ASMs during the prior 90 days were retrospectively identified. Only patients with focal epilepsy and with 12-month follow-up after initiating BRV were included in the current analysis. Data on demographics, clinical history, type of seizures and epilepsy [14], etiology, previous/concomitant ASMs, and baseline seizure frequency (monthly seizure frequency during the 3 months before starting BRV) were collected. Concomitant ASMs were classified, according to their mechanism of action, into sodium channel blockers (SCBs; carbamazepine, phenytoin, lamotrigine, oxcarbazepine, eslicarbazepine acetate, lacosamide, rufinamide) and no SCBs (any other ASM); patients in the SCB group were those receiving at least one SCB, whereas those in the no SCB group did not take any SCB. Concomitant ASMs were classified as strong enzyme-inducing ASMs (EiASMs), i.e., carbamazepine, phenytoin, phenobarbital, and primidone, being the major EiASMs that stimulate the rate of metabolism of most coadministered ASMs [15], and no strong EiASMs (any other ASM); patients were described as taking strong EiASMs if they were taking at least one strong EiASM during BRV treatment. Prospectively collected data on seizure occurrence, adverse events (AEs) and drug withdrawal were retrieved from patient seizures diaries and clinical records; visits at 3, 6, and 12 months were performed as standard practice when a new ASM was initiated. Exclusion criteria were history of alcoholism, drug abuse, conversion disorders or other non-epileptic ictal events.

Effectiveness outcomes included the rates of seizure freedom, seizure response (≥50% reduction in baseline monthly seizure frequency), seizure worsening (>25% increase in monthly seizure frequency relative to baseline, unless patients were seizure-free during the 3 months before starting BRV) and treatment discontinuation at 12 months. Further analyses were performed using data obtained from the visits at 3 and 6 months. Seizure freedom at each time point was defined as the occurrence of no seizures since at least the previous visit; at 12 months, it was considered as no seizures during the preceding 6 months, and at 3 and 6 months was defined as lack of seizures since baseline or the 3-month visit, respectively. Safety and tolerability outcomes included the rate of treatment discontinuation due to AEs and the incidence of AEs considered BRV-related by participating physicians.

Exploratory analyses were performed to evaluate the impact of LEV status, i.e., prior LEV treatment (never LEV use, prior LEV use and discontinuation/switch to BRV due to insufficient efficacy, prior LEV use and discontinuation/switch to BRV due to AEs), concomitant use of strong EiASMs, and concomitant use of SCBs.

2.2 Statistical Analysis

Values were presented as median [interquartile range] for continuous variables and number (%) of subjects for categorical variables. Comparisons were made using the Mann–Whitney test, Dunn's test or Chi-square test, as appropriate. Simple and multivariable logistic regression models were performed to identify baseline characteristics of patients associated with 12-month seizure freedom. Preselected independent variables were age, sex, number of previous ASMs, number of concomitant ASMs, baseline monthly seizure frequency, and LEV status [16–18]; age, number of previous ASMs, number of concomitant ASMs, and baseline monthly seizure frequency were entered into regression models as continuous variables, and sex and LEV status as categorical variables.

Results were considered significant for p values < 0.05 (two-sided). Data analysis was performed using STATA/IC 13.1 (StataCorp LLC, College Station, TX, USA). The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [19].

3 Results

Of 1325 patients initially identified, 71 were excluded as diagnosed with generalized, combined or unknown epilepsy and 225 because follow-up after initiating BRV was < 1 year at the data cut-off point for this report. Accordingly, 1029 patients with focal epilepsy were included. The median age of the patients was 45 years [33–56], and 487 (47.3%) were males. Patients had a history of a median of 5 [3–8] lifetime ASMs, and BRV was added to a median of 2 [1–3] concomitant ASMs; the most common concomitant ASMs were carbamazepine, valproic acid and lacosamide. The median baseline seizure frequency was 5 [2–18], and 35 (3.4%) patients were seizure-free during the 3 months before starting BRV. The baseline characteristics of participants are summarized in Table 1 and details about the concomitant ASMs are shown in Table 2.

The median daily dose of BRV at 3 months was 100 mg [100–200], 150 mg [100–200] at 6 months, and 150 mg [100–200] at 12 months. At 12 months, 169 (16.4%) patients were seizure-free and 383 (37.2%) patients had their seizure

frequency reduced by 50% or more in comparison with baseline. The rates of seizure response, seizure freedom and seizure worsening at 3 and 6 months are shown in Fig. 1.

The baseline characteristics of patients by LEV status are presented in Table 3. Patients with prior LEV use and withdrawal due to insufficient efficacy had a longer duration of epilepsy, were treated with more concomitant ASMs, and had higher seizure frequency at baseline than LEV-naive patients. At 12 months, the rate of seizure freedom was 59/265 (22.3%) in LEV-naive patients, 34/481 (7.1%) in patients with prior LEV use and discontinuation/switch to BRV due to insufficient efficacy, and 67/215 (31.2%) in patients with prior LEV use and discontinuation/switch to BRV due to AEs ($p < 0.001$); the corresponding values for ≥50% seizure frequency reduction were 47.9%, 29.7%, and 42.8%, respectively ($p < 0.001$).

At 12 months, there were no statistically significant differences in seizure freedom (15.6% vs. 18.8%; $p = 0.199$) and seizure responder rates (38.2% vs. 37.4%; $p = 0.816$) between patients receiving concomitant strong EiASMs versus patients treated with no strong EiASMs.

The baseline characteristics of patients by concomitant use of SCBs are shown in Table 4. Patients concomitantly taking SCBs had a longer duration of epilepsy, had been exposed to a higher number of prior ASMs, were treated with more concomitant ASMs, were more commonly treated with strong EiASMs, and had higher seizure frequency at baseline than patients concomitantly treated with no SCBs. There was a trend towards a higher 12-month seizure freedom rate in patients treated with add-on BRV and concomitant SCBs, but this was not statistically significant ($p = 0.341$), and there was a statistically significant ($p = 0.006$) higher number of responders to BRV in patients who were receiving SCBs than in those receiving no SCBs (Fig. 2).

Age [odds ratio (OR) 1.014, 95% confidence interval (CI) 1.002–1.026; $p = 0.027$], number of previous ASMs (OR 0.75, 95% CI 0.68–0.82; $p < 0.001$), baseline monthly seizure count (OR 0.94, 0.91–0.97; $p < 0.001$) and history of LEV withdrawal for tolerability issues (OR 2.25, 1.40–3.60; $p = 0.001$) were independent predictors of 12-month seizure freedom; patients with older age, lower number of lifetime ASMs, lower baseline seizure frequency and prior

Table 1 Baseline characteristics of patients

Characteristics	Patients [$n = 1029$]
Age, years	45 (33–56)
Male sex	487 (47.3)
Age at epilepsy onset, years [$N = 1028$[a]]	13 (6–26)
Duration of epilepsy, years [$N = 1028$[a]]	25 (13–38)
Type of seizure [$N = 916$[a]]	
Focal onset	679 (74.1)
Focal to bilateral tonic-clonic	171 (18.7)
Focal onset and focal to bilateral tonic-clonic[b]	66 (7.2)
Etiology	
Structural	553 (53.7)
Genetic	40 (3.9)
Immune	11 (1.1)
Infectious	28 (2.7)
Unknown	397 (38.6)
Number of previous ASMs [$N = 1023$[a]]	5 (3–8)
Levetiracetam status [$N = 1022$[a]]	
Never used	265 (25.9)
Prior use/prescribed at baseline	757 (74.1)
Number of concomitant ASMs [$N = 1028$[a]]	2 (1–3)
Concomitant use of EiASM(s) at baseline [$N = 901$[a]]	487 (54.1)
Concomitant use of SCB(s) at baseline [$N = 901$[a]]	771 (85.6)
Baseline monthly seizure frequency[c]	5 (2–18)

Data are expressed as median (IQR) for continuous variables, and *n* (%) for categorical variables

ASMs antiseizure medications, *BRV* brivaracetam, *EiASMs* enzyme-inducing ASMs, *IQR* interquartile range, *SCBs* sodium channel blockers

[a]*N* represents the total number of patients for whom data in question were available

[b]Patients presenting both focal onset and focal to bilateral tonic-clonic seizures

[c]Based on the number of seizures during the 90 days before starting adjunctive BRV

Table 2 Concomitant antiseizure medications

Concomitant antiseizure medication	Patients ($N = 901$[a])
Carbamazepine	359 (39.8)
Valproic acid	209 (23.2)
Lacosamide	176 (19.5)
Phenobarbital	172 (19.1)
Lamotrigine	170 (18.9)
Perampanel	112 (12.4)
Benzodiazepines	102 (11.3)
Oxcarbazepine	83 (9.2)
Topiramate	76 (8.4)
Zonisamide	53 (5.9)
Eslicarbazepine acetate	38 (4.2)
Phenytoin	32 (3.6)
Primidone	26 (2.9)
Pregabalin	18 (2.0)
Rufinamide	13 (1.4)

Data are expressed as *n* (%)

[a]*N* represents the total number of patients for whom data in question were available. Concomitant antiseizure medications taken by > 1% of patients are reported

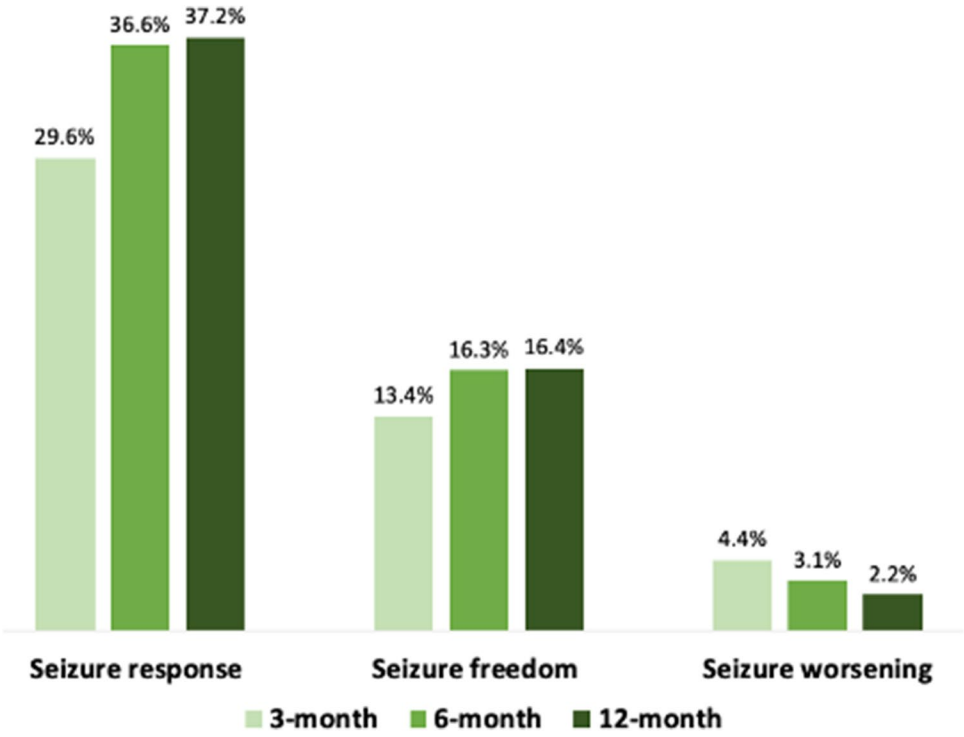

Fig. 1 Clinical response to adjunctive brivaracetam. Rates of seizure response, seizure freedom and seizure worsening at 3, 6 and 12 months are reported. Seizure response was defined as a ≥ 50% reduction in seizure frequency in comparison with baseline seizure frequency, while seizure worsening was defined as an increase in seizure frequency of > 25% in comparison with baseline seizure frequency

discontinuation of LEV due to adverse effects had a higher likelihood of being free from seizures (Table 5).

During the 1-year study period, 265 (25.8%) patients of the cohort discontinued BRV. The reasons for BRV withdrawal were insufficient efficacy (n = 159, 15.5%), AEs (n = 99, 10.0%), and a combination of both (n = 5, 0.5%); in one case, BRV was discontinued due to the patient's request and one patient died due to a cause unrelated to the treatment. Of 265 patients who withdrew BRV, 120 (45.3%) had their treatment discontinued at 3 months, 71 (26.8%) at 6 months, and 74 (27.9%) at 12 months (Fig. 3).

The rate of treatment discontinuation for any cause was lower in patients who were LEV-naive (22.3%) or had a history of LEV withdrawal due to adverse effects (18.6%) than in those with prior LEV use and discontinuation/switch to BRV due to insufficient efficacy (30.6%; p = 0.001). Drug withdrawal due to poor efficacy occurred less commonly among patients who had never tried LEV (13.2%) or had a history of LEV discontinuation due to adverse effects (8.8%) than in patients who had used LEV and discontinued it due to insufficient efficacy (20.0%; p < 0.001). There were no statistically significant differences in the rates of BRV withdrawal for AEs according to LEV history (p = 0.841), and there were no statistically significant differences in the proportions of patients who withdrew BRV for any cause (p = 0.763), insufficient efficacy (p = 0.090) or poor tolerability (p = 0.173) on the basis of concomitant use of strong EiASMs. Furthermore, there were no statistically significant differences in the rate of BRV withdrawal due to any cause (p = 0.188) or insufficient efficacy (p = 0.899) according to the concomitant use of SCBs; treatment discontinuation due to AEs was less common in patients treated with BRV and concomitant SCBs than in patients treated with BRV and no SCBs (8.8% vs. 14.6%; p = 0.038).

AEs were reported by 30.1% of patients and were rated as mild (75.4%), moderate (24.2%) or severe (0.4%) in intensity. The most common AEs observed in the study cohort included somnolence (6.6%), nervousness and/or agitation (5.9%), vertigo (3.6%), fatigue (3.1%), and headache (2.6%) (Table 6). Among patients who switched from LEV to BRV due to AEs and for whom tolerability follow-up data were available, 3/26 (11.5%) experienced new or persisting AEs.

There were no statistically significant differences in the occurrence of AEs according to LEV history (p = 0.833) and use of concomitant strong EiASMs (p = 0.071); AEs were less commonly observed in patients treated with BRV and concomitant SCBs than in patients treated with BRV and no SCBs (28.9% vs. 39.8%; p = 0.017).

4 Discussion

The BRIVAFIRST provided interesting findings about the use of BRV in patients with focal epilepsy. The main results included (1) the large number of patients enrolled within the frame of an integrated national network; (2) the effectiveness of BRV in patients with focal seizures treated according

Table 3 Baseline characteristics of patients according to levetiracetam status

Characteristics	LEV-naïve [$n = 265$]	LEV prior—insufficient efficacy [$n = 481$]	LEV prior—adverse events [$n = 215$]
Age, years	44 (32–57)	44 (32–54)‡	48 (37–61)*
Male sex	127 (47.9)	218 (45.3)	111 (51.6)
Age at epilepsy onset, years [$N = 960$[a]]	14 (5–29)	12 (5–20)*‡	18 (7–44)*
Duration of epilepsy, years [$N = 960$[a]]	23 (10–36)	26 (16–39)*‡	20 (9–37)
Type of seizure ($N = 855$[a])			
Focal onset	176 (74.3)	318 (75.2)	142 (72.8)
Focal to bilateral tonic-clonic	52 (21.9)	71 (16.8)	34 (17.4)
Focal onset and focal to bilateral tonic-clonic[b]	9 (3.8)	34 (8.0)	19 (9.7)
Etiology			
Structural	148 (55.9)	233 (48.4)	132 (61.4)
Genetic	8 (3.0)	17 (3.5)	9 (4.2)
Immune	2 (0.8)	5 (1.0)	4 (1.9)
Infectious	7 (2.6)	15 (3.1)	2 (0.9)
Unknown	100 (37.7)	211 (43.9)	68 (31.6)
Number of previous ASMs [$N = 956$[a]]	3 (2–5)	7 (5–9)*‡	5 (3–7)*
Number of concomitant ASMs [$N = 960$[a]]	2 (1–2)	2 (2–3)*‡	2 (1–3)
Concomitant use of EiASM(s) at baseline [$N = 839$[a]]	113 (48.7)	237 (57.3)	107 (55.4)
Concomitant use of SCB(s) at baseline [$N = 839$[a]]	193 (83.2)	359 (86.7)	172 (89.1)
Baseline monthly seizure frequency[c]	5 (2–15)	7 (3–20)*‡	4 (1–12)*

Data are expressed as median (IQR) for continuous variables, and *n* (%) for categorical variables

ASMs antiseizure medications, *BRV* brivaracetam, *EiASMs* enzyme-inducing ASMs, *IQR* interquartile range, *LEV* levetiracetam, *SCBs* sodium channel blockers

*$p < 0.05$ versus the LEV-naive group

‡$p < 0.05$ versus the LEV prior—adverse events group

[a]*N* represents the total number of patients for whom data in question were available

[b]Patients presenting both focal onset and focal to bilateral tonic-clonic seizures

[c]Based on the number of seizures during the 90 days before starting adjunctive BRV

to everyday clinical practice, including patients who have previously failed LEV; and (3) the higher responder rate observed among patients treated with BRV and concomitant SCBs than in those not receiving SCBs.

Among the studies aimed at evaluating the response to BRV add-on therapy in real-world clinical practice, the BRIVAFIRST is characterized by a larger population. This experience stemmed from the belief that a functional network engaged in building reliable evidence from real-world data may actually contribute to characterize the drug profile. Typically, regulatory trials deviate markedly from routine clinical practice, and the restrictive eligibility criteria, rigid titration and dosing schedules, and short follow-up duration limit the generalizability of the results [20]. In this regard, data generated in a real-life setting reflect physicians' experience and daily challenges. Studies performed in a naturalistic context do not only assess the efficacy and tolerability of ASMs under real-world conditions but also offer new insights on issues not addressed or left unanswered by pivotal trials.

In the cohort of patients included in the BRIVAFIRST who have a long disease duration, a considerable number of previously failed ASMs, and a high number of ongoing ASMs, the rates of seizure freedom and seizure response at 12-month follow-up were 16% and 37%, respectively. These figures indicate the efficacy of BRV to control seizures when added to the pre-existing therapeutic regimen in everyday clinical practice in patients with difficult-to-treat epilepsy, and confirm previous evidence [21–28]. In line with other ASMs [29, 30], an inverse relationship between response to adjunctive BRV and the number of lifetime medications was observed, confirming that the higher the number of failed treatments, the lower the likelihood that the patient may benefit from subsequent interventions [31]. Likewise, the higher seizure frequency at baseline can act as a marker of the intrinsic severity of epilepsy.

Age was also an independent predictor of seizure freedom, with older age being associated with a greater probability of seizure freedom at 1 year after starting BRV.

Table 4 Baseline characteristics of patients according to concomitant use of sodium channel blockers

Characteristics	Concomitant use of SCBs [$n = 771$]	Concomitant use of no SCBs [$n = 130$]	p value
Age, years	45 (34–56)	46 (30–63)	0.637
Male sex	364 (47.2)	59 (45.4)	0.699
Age at epilepsy onset, years	13 (6–26)	15 (7–40)	0.065
Duration of epilepsy, years	25 (13–38)	20 (9–33)	0.006
Type of seizure [$N = 857$[a]]			0.135
Focal onset	543 (73.9)	81 (66.4)	
Focal to bilateral tonic-clonic	136 (18.5)	32 (26.2)	
Focal onset and focal to bilateral tonic-clonic[b]	56 (7.6)	9 (7.4)	
Etiology			< 0.001
Structural	425 (55.1)	53 (40.8)	
Genetic	20 (2.6)	13 (10.0)	
Immune	7 (0.9)	3 (2.3)	
Infectious	25 (3.2)	3 (2.3)	
Unknown	294 (38.1)	58 (44.6)	
Number of previous ASMs [$N = 898$[a]]	5 (3–8)	4 (2–8)	0.010
Number of concomitant ASMs	2 (1–3)	1 (1–2)	< 0.001
Concomitant use of EiASM(s) at baseline	448 (58.1)	39 (30.0)	< 0.001
Baseline monthly seizure frequency[c]	6 (2–20)	4 (1–10)	0.002

Data are expressed as median (IQR) for continuous variables, and *n* (%) for categorical variables

ASMs antiseizure medication, *BRV* brivaracetam, *EiASMs* enzyme-inducing ASMs, *IQR* interquartile range, *SCBs* sodium channel blockers

[a]*N* represents the total number of patients for whom data in question were available

[b]Patients presenting both focal onset and focal to bilateral tonic-clonic seizures

[c]Based on the number of seizures during the 90 days before starting adjunctive BRV

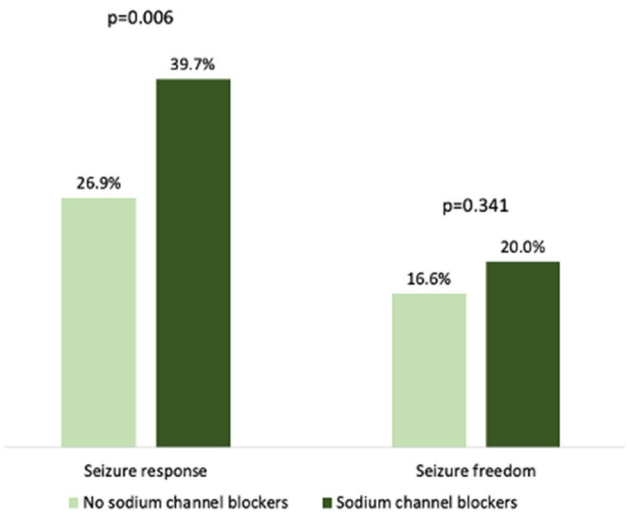

Fig. 2 Add-on brivaracetam efficacy according to concomitant use of sodium channel blockers. Rates of seizure response and seizure freedom at 12 months are reported according to concomitant use of sodium channel blockers (sodium channel blockers, $n = 771$; no sodium channel blockers, $n = 130$). Seizure response was defined as a ≥ 50% reduction in seizure frequency in comparison with baseline seizure frequency

Consistent with the greater proportion of responders already observed in patients aged ≥ 65 years than in the younger subgroup [24], BRV might be considered as a viable choice for the treatment of focal seizures in the elderly. Differences in the epilepsy aetiology and metabolism across the classes of age need to be investigated to identify possible explanations, including drug blood levels that may be higher in elderly patients.

Given the structural similarities between BRV and LEV, the treatment efficacy according to prior LEV exposure is a matter of great interest and this study built up prior evidence through subgroup analyses by LEV historical use and reasons for LEV discontinuation. Adjunctive BRV was associated with seizure frequency reduction, both in patients with and patients without prior use of LEV. Of note, around 30% of patients with prior LEV use who discontinued it or switched to BRV due to insufficient efficacy had a reduction in baseline seizure frequency of ≥ 50%, and 7% of patients were seizure-free at 12 months. The rates of seizure freedom and seizure response also highlighted the greater efficacy of BRV among LEV-naive patients than in patients who had previously discontinued LEV due to poor efficacy. It is worth noting that patients with prior LEV use and withdrawal due to insufficient efficacy had a longer duration of epilepsy,

Table 5 Association between baseline characteristics and seizure freedom at 12 months

Dependent variable	Unadjusted		Adjusted[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	1.03 (1.02–1.04)	< 0.001	1.014 (1.002–1.026)	0.027
Sex	1.26 (0.90–1.75)	0.177	1.22 (0.83–1.80)	0.319
Number of previous ASMs	0.67 (0.62–0.72)	< 0.001	0.75 (0.68–0.82)	< 0.001
Number of concomitant ASMs	0.44 (0.36–0.56)	< 0.001	0.83 (0.63–1.10)	0.190
Baseline monthly seizure frequency	0.90 (0.87–0.93)	< 0.001	0.94 (0.91–0.97)	< 0.001
Levetiracetam status[b]				
LEV prior—insufficient efficacy	0.27 (0.17–0.42)	< 0.001	0.66 (0.39–1.11)	0.117
LEV prior—adverse events	1.58 (1.05–2.38)	0.028	2.25 (1.40–3.60)	0.001

Values are from logistic regression models

ASMs antiseizure medications, *CI* confidence interval, *LEV* levetiracetam, *OR* odds ratio

[a]Adjusted for age, sex, number of previous ASMs, number of concomitant ASMs, baseline monthly seizure frequency, and LEV status

[b]LEV-naive group as the reference

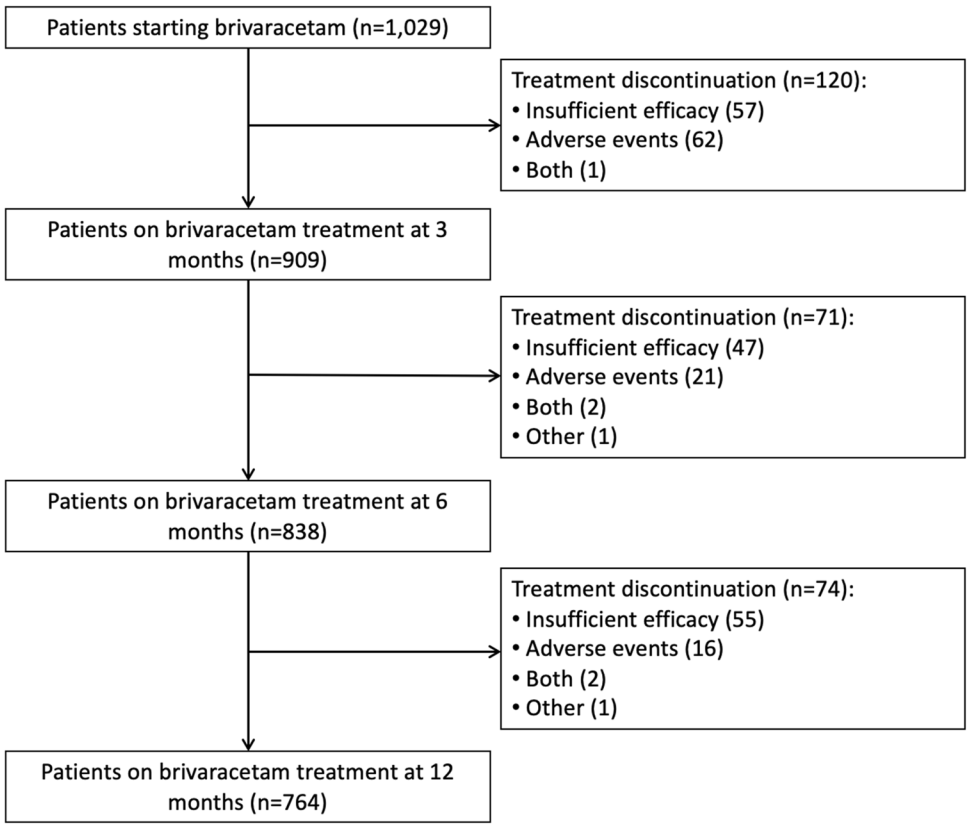

Fig. 3 Patient disposition according to brivaracetam discontinuation

were treated with a higher number of concomitant ASMs, and had a higher seizure frequency at baseline than LEV-naive patients, suggesting that they could represent a group of more difficult-to-treat patients. However, the lack of information about serum concentrations of LEV could not allow evaluation of the actual status of treatment and whether there were cases of undertreatment. Similarly, in a pooled analysis of data from RCTs, BRV had greater efficacy in LEV-naïve patients than in patients with prior exposure to other commonly prescribed ASMs, including not only LEV but also carbamazepine, lamotrigine, and topiramate [32]. These findings strongly suggest that failure to respond to LEV does not preclude BRV treatment use. Despite similarities in their chemistry, differences exist between BRV and LEV.

Table 6 Adverse events with brivaracetam treatment

Patients with adverse events	
N[a]	877
n (%)	264 (30.1)
Most frequently reported adverse events (reported by ≥ 1% of patients)	
N[a]	852
Somnolence	56 (6.6)
Nervousness and/or agitation	50 (5.9)
Vertigo	31 (3.6)
Fatigue	26 (3.1)
Headache	22 (2.6)
Aggressiveness	20 (2.3)
Mood change	20 (2.3)
Dizziness	19 (2.2)
Sleep disturbances	15 (1.8)
Memory disturbance	14 (1.6)

Data are expressed as *n* (%)

AEs reported by fewer than 1% of patients: nausea/vomiting, tremor (all $n = 8$, 0.9%), stomach pain ($n = 7$, 0.8%), disturbances in attention/concentration ($n = 6$, 0.7%), anxiety, diplopia/blurred vision (all $n = 5$, 0.6%), weight increase ($n = 4$, 0.5%), skin disorders, hair loss (all $n = 3$, 0.4%), fever, pharyngodynia, hyporexia (all $n = 2$, 0.2%), urinary disturbances, weight decrease, psychosis, tics, confusion, acouphene, constipation, abdominal pain (all $n = 1$, 0.1%)

[a]*N* represents the total number of patients for whom the data in question were available

Compared with LEV, BRV has higher affinity and selectivity for SV2A, and the differential interactions of the drugs with the target protein may provide the molecular correlate to their distinct pharmacodynamic properties and efficacy profiles [5]. Furthermore, the traditional modes of action of other ASMs do not contribute significantly to the antiseizure properties of BRV that, in contrast with LEV, have no effect on the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and high-voltage-activated calcium channels at therapeutically relevant concentrations [33].

During the 1-year study period, the overall rate of treatment discontinuation was about 25%, which was similar to that observed in other studies focusing on BRV and newer ASMs in clinical practice, including eslicarbazepine, perampanel, and lacosamide [21–29, 34–36]. The main reason for drug withdrawal was inadequate efficacy, and BRV was interrupted within the first 3 months of treatment in almost half of the cases. Around one-third of patients reported AEs throughout the 12-month follow-up, which were mostly mild in intensity. The most frequently observed AEs were somnolence, vertigo, fatigue and headache, which substantially overlap the profile of adverse effects of the majority of the ASMs [37]; nervousness and agitation were reported by 6% of patients and were the most common psychiatric AEs. These data confirmed the overall favourable tolerability profile of BRV when added to concomitant ASMs, and matched the already available evidence from both randomized and open-label studies [13, 21–28]. A slow-escalation dosing regimen may represent a useful strategy to avoid or minimize adverse effects as somnolence and fatigue.

Interesting and novel observations compared with prior studies emerged regarding the association between BRV and concomitant ASMs. Interestingly, the combination of BRV with SCBs, rather than no SCBs, resulted in better efficacy and tolerability and was associated with a higher rate of seizure responders and lower rates of AEs and treatment withdrawal due to AEs. To date, there are no experimental and clinical data about any advantageous combinations of BRV with other ASMs. As a general rule, favourable combinations usually consist of ASMs with different mechanisms of action [38], and additive or synergic efficacy without increased toxicity has been found when combining LEV with carbamazepine, oxcarbazepine and lacosamide [39]. Additional studies are warranted to specifically address this preliminary evidence regarding the favourable association of BRV with SCBs.

BRV has a low risk of clinically relevant DDIs. Strong EiASMs such as carbamazepine, phenytoin and phenobarbital have been shown to moderately reduce BRV plasma levels in the absence of a significant influence on clinical response and without the need for dose adjustment [7]. In the BRIVAFIRST, no statistically significant differences in the rates of seizure freedom, seizure responder, and AEs were found between patients receiving concomitant strong EiASMs and patients not treated with strong EiASMs. Although data on plasma drug concentrations were not available, these findings provided indications of a favourable pharmacokinetic profile of BRV, which can represent an advantageous characteristic in the case of poly drug regimens.

4.1 Strengths and Limitations

The main strengths of the BRIVAFIRST included the recruitment at multiple centres and the large sample size, which allowed exploratory subgroup analyses. Furthermore, the real-world setting, which reflects physicians' experience and judgements in adapting doses and discontinuing individual ASMs according to efficacy and tolerability concerns, provided a high degree of external validity and generalizability of the findings to everyday clinical practice. The study also presented some limitations, such as its open-label design and retrospective nature, which may have introduced potential sources of biases, the lack of details about specific etiologies and seizure frequency data by seizure subtypes, and the unavailability of serum levels of BRV and concomitant ASMs, which prevented exploring the individual interactions between drugs. The collection of AEs

based on records of clinical visits rather than standardized questionnaires might have resulted in possible underreporting. Furthermore, the absence of a control group undergoing treatment with an alternative therapeutic option prevents drawing any conclusions about the comparative effectiveness of BRV and other ASMs.

5 Conclusion

The findings of the BRIVAFIRST provided real-world evidence on the effectiveness of BRV in patients with focal epilepsy irrespective of LEV history and concomitant ASMs, and suggested favourable therapeutic combinations. Further research is needed to explore the actual potential of BRV in specific aetiologies and epilepsy syndromes and also as early-add on treatment, and to provide more information for guiding clinical decisions.

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Consent to Participate Informed consent was obtained from every patient and/or their parent or legal representative.

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