Received: 13 February 2022 | Revised: 6 March 2022 | Accepted: 9 March 2022

DOI: 10.1111/epi.17223

Epilepsia®

BRIEF COMMUNICATION

Sustained seizure freedom with adjunctive brivaracetam in patients with focal onset seizures

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Abstract

The maintenance of seizure control over time is a clinical priority in patients with epilepsy. The aim of this study was to assess the sustained seizure frequency reduction with adjunctive brivaracetam (BRV) in real-world practice. Patients with focal epilepsy prescribed add-on BRV were identified. Study outcomes included sustained seizure freedom and sustained seizure response, defined as a

BRIVAFIRST Group members are presented in Appendix 1.

100% and a ≥50% reduction in baseline seizure frequency that continued without interruption and without BRV withdrawal through the 12-month follow-up. Nine hundred ninety-four patients with a median age of 45 (interquartile range = 32–56) years were included. During the 1-year study period, sustained seizure freedom was achieved by 142 (14.3%) patients, of whom 72 (50.7%) were seizure-free from Day 1 of BRV treatment. Sustained seizure freedom was maintained for ≥6, ≥9, and 12 months by 14.3%, 11.9%, and 7.2% of patients from the study cohort. Sustained seizure response was reached by 383 (38.5%) patients; 236 of 383 (61.6%) achieved sustained ≥50% reduction in seizure frequency by Day 1, 94 of 383 (24.5%) by Month 4, and 53 of 383 (13.8%) by Month 7 up to Month 12. Adjunctive BRV was associated with sustained seizure frequency reduction from the first day of treatment in a subset of patients with uncontrolled focal epilepsy.

KEYWORDS

antiseizure medication, brivaracetam, focal seizures, seizure freedom, sodium channel blockers

1 | INTRODUCTION

Brivaracetam (BRV) is a third-generation antiseizure medication (ASM) that acts as a selective ligand for synaptic vesicle protein 2A, with similar chemical structure and higher binding affinity than levetiracetam (LEV). In randomized controlled trials (RCTs), BRV reduced seizure frequency when added to pre-existing ASMs in patients with drug-resistant focal epilepsy.[1]

The aim of this study was to assess the sustained clinical response to adjunctive BRV in patients with focal seizures treated in the setting of real-world practice.

2 | MATERIALS AND METHODS

2.1 | Participants

BRIVAFIRST (BRIVAracetam add-on First Italian netwoRk STudy) was a retrospective study conducted across 63 Italian centers.[2] Adult patients (age ≥ 16 years) attending participating centers who were prescribed BRV (March 2018 to March 2020) and were on stable treatment with ≥1 ASM during the prior 90 days were retrospectively identified. Only patients with focal epilepsy, 12-month follow-up after initiating BRV, and at least one seizure during the 3 months before introducing BRV were included in the current analysis. Data on demographics, clinical history, type of seizures and epilepsy,[3] 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 non-SCBs (any other ASM); patients in the SCB group were those receiving at least one SCB, whereas those in the non-SCB group did not take any SCB. Seizure occurrence, adverse events (AEs), and drug withdrawal were retrieved from clinical records of 3-, 6-, and 12-month follow-up visits, which represent standard practice when a new ASM is initiated. Exclusion criteria were history of alcoholism, drug abuse, conversion disorders, and other nonepileptic ictal events.

Primary outcome was sustained seizure freedom (SSF), defined as a 100% reduction in baseline seizure frequency that continued without interruption from the first time it was achieved through the 12-month follow-up without BRV withdrawal. Secondary outcome was sustained seizure response (SSR), defined as a ≥50% reduction in baseline seizure frequency that continued without interruption from the first time it was achieved through 12 months without BRV withdrawal. The time of achievement of SSF and SSR was established using data at visits at 3, 6, and 12 months. The rate and reasons for treatment discontinuation and the incidence of AEs considered BRV-related by physicians were also considered. Exploratory analyses were performed to evaluate the impact of concomitant SCB use, history of LEV use, and advanced age (≥65 years) on SSF and SSR outcomes.

2.2 | Statistical analysis

Values are presented as mean (±SD) or median (interquartile range) for continuous variables and

number (percent) of subjects for categorical variables. Comparisons between categorical variables were made using chi-squared test. Simple and multivariate logistic regression models were performed to identify baseline characteristics of patients associated with SSF and SSR. Selected independent variables were age, number of previous ASMs, number of concomitant ASMs, concomitant use of SCBs, and baseline monthly seizure frequency.[4,5] Results were considered significant for p values < .05 (two sided). Data analysis was performed using Stata/IC 13.1 (StataCorp).

2.3 | Standard protocol approval

The study was approved by the ethical committee of Sapienza University, Rome, Italy and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from each patient or a legal representative.

2.4 | Data availability

Anonymized data will be shared by request from any qualified investigator.

3 | RESULTS

Of 1325 patients initially identified, 71 patients were excluded as diagnosed with generalized, combined, or unknown epilepsy, 225 because follow-up was <1 year at the time of the current analysis and 35 because they were seizure-free at baseline. Accordingly, 994 patients were included. The median age was 45 (32–56) years, and there were 100 elderly patients (10.1%). Baseline characteristics of participants are summarized in Table 1. Baseline characteristics of patients according to concomitant use of SCB(s) at baseline and LEV status are shown in Table S1 and Table S2. Within the subgroup of patients not receiving SCBs at the time of BRV initiation, 23 (71.9%) of 32 patients for whom this information was available had no history of prior use of SCBs.

In the study cohort, the median daily dose of BRV was 100 (100–200) mg at 3 months, 150 (100–200) mg at 6 months, and 150 (100–200) mg at 12 months. During the 1-year study period, SSF was achieved by 142 (14.3%) patients; 72 (7.2%) patients were seizure-free from Day 1, 46 (4.6%) from Month 4, and 24 (2.4%) from Month 7 (Figure 1A). Among the patients reaching SSF, 50.7% were seizure-free from Day 1 of treatment (Figure 1B). Sustained seizure freedom was maintained for ≥6, ≥9, and 12 months by 14.3%, 11.9%, and 7.2% patients (Figure 1C). Sustained seizure response was reached by 383 (38.5%) patients, and 236 (23.7%) were sustained seizure responders from Day 1 (Figure 1A). Among the patients who reached SSR, 61.6% achieved it by Day 1 (Figure 1B). Sustained seizure response status was maintained for ≥6, ≥9, and 12 months by 38.5%, 33.2%, and 23.7% of patients (Figure 1C).

The overall rate of SSF was 15.2% when BRV was added to concomitant SCBs and 12.2% in patients treated with no SCBs (p = .401); the rate of SSR was significantly higher among patients receiving than in those not receiving SCBs (40.7% vs. 30.4%; p = .036).

Age, the number of previous ASMs, the concomitant use of SCBs, and baseline monthly seizure count were independent predictors of SSF and SSR, with older age, lower number of lifetime ASMs, concomitant administration of SCBs, and lower baseline seizure frequency being associated with a higher likelihood of achieving SSF (Table S3) and SSR (Table S4).

TABLE 1 Baseline characteristics of patients

Characteristic	Patients, n = 994
Age, years	45 (32–56)
Male sex	469 (47.2)
Age at epilepsy onset, years, N = 993[a]	13 (5–24)
Duration of epilepsy, years, N = 993[a]	25 (14–38)
Type of seizures, N = 884[a]	
Focal onset	657 (74.3)
Focal to bilateral tonic–clonic	165 (18.7)
Focal onset and focal to bilateral tonic–clonic	62 (7.0)
Etiology	
Structural	532 (53.5)
Genetic	38 (3.8)
Immune	10 (1.0)
Infectious	27 (2.7)
Unknown	387 (39.0)
Number of previous ASMs, N = 988[a]	6 (3–8)
Number of concomitant ASMs, N = 993[a]	2 (1–3)
Concomitant use of SCB(s) at baseline, N = 867[a]	752 (86.7)
Levetiracetam status, N = 987[a]	
Never used	260 (26.3)
Prior use/prescribed at baseline	727 (73.7)
Baseline monthly seizure frequency[b]	6 (3–20)

Note: Data are median (interquartile range) for continuous variables, and n (%) for categorical variables.

Abbreviations: ASM, antiseizure medication; SCB, sodium channel blocker.

[a]N refers to the total number of patients for whom data in question were available.

[b]Based on the number of seizures during the 90 days before starting adjunctive brivaracetam.

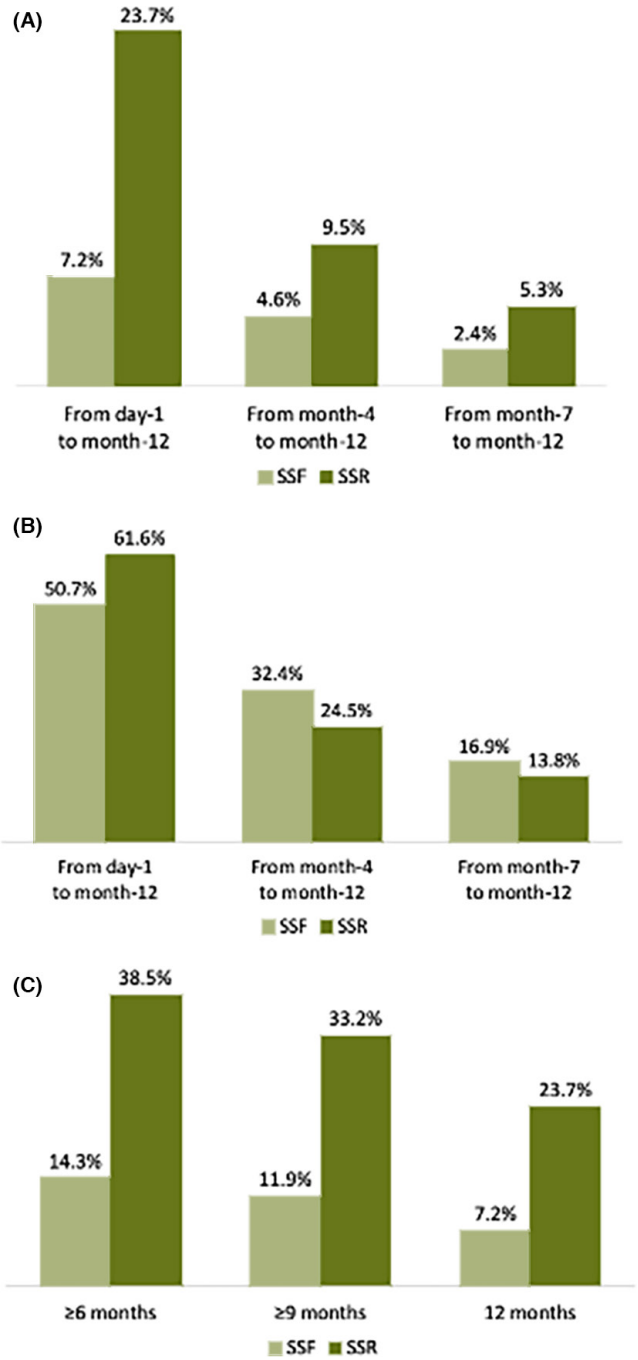

FIGURE 1 Sustained seizure freedom (SSF) and sustained seizure response (SSR) outcomes. (A) Proportions of patients from the study cohort who were seizure-free and seizure responders from Day 1, Month 4, and Month 7 to Month 12. (B) Proportions of patients reaching SSF and SSR who were seizure-free and seizure responders from Day 1, Month 4, and Month 7 to Month 12. (C) Proportions of patients from the study cohort who maintained SSF and SSR for ≥6, ≥9, and 12 months

In the analysis by LEV status, the overall rate of SSF with adjunctive BRV during the 1-year study period was 21.5% in patients who had never been treated with LEV and 11.7% in patients who had a history of LEV use ($p < .001$); the rate of SSR was significantly higher among LEV-naïve patients than patients who had taken LEV (48.9% vs. 34.7%; $p < .001$).

In the analysis by age, the overall rate of SSF with adjunctive BRV during the 1-year study period was 27.0% in elderly patients and 12.9% in younger patients ($p < .001$); the rate of SSR was significantly higher among elderly than younger patients (49.0% vs. 37.4%; $p = .023$).

BRV was discontinued by 259 (26.1%) patients; the reasons were insufficient efficacy ($n = 159/259$, 61.4%), AEs ($n = 93/259$, 35.9%), and a combination of both ($n = 5/259$, 1.9%); in one case, BRV was discontinued due to the patient's request, and one patient died from a cause unrelated to treatment.

AEs were reported by 30.1% of the patients and rated as mild (74.8%), moderate (24.8%), and severe (.4%, corresponding to one case of depressive mood change). The most common AEs were somnolence (6.7%), nervousness and/or agitation (5.7%), vertigo (3.4%), and fatigue (3.2%; Table 2).

4 | DISCUSSION

In a real-world cohort of patients with uncontrolled focal epilepsy, approximately 15% and 40% of the population treated with adjunctive BRV reached SSF and SSR, and sustained seizure frequency reduction was achieved on the first day of treatment in the majority of the cases.

Seizure freedom is recognized as the goal of epilepsy treatment by patients and caregivers.[6] Quality of life in patients with treatment-refractory epilepsy is not influenced by reductions in seizure frequency that does not meet seizure freedom,[6] and the International League Against Epilepsy emphasizes seizure freedom as a major study endpoint.[6] Despite its importance, many trials fail to report the seizure freedom outcome, and great heterogeneity exists in its definition.[6] Importantly, the maintenance of seizure freedom is a clinical priority, and it remains uncertain whether short-term seizure freedom observed in pivotal trials is a predictor of longer term freedom. In addition, the methodology usually used to analyze clinical trial data counts even patients withdrawn from therapy before the end of the treatment period and potentially overestimates seizure freedom rate.[7] Responder rate is also accepted as a regulatory outcome, but there is no requirement for seizure reduction to be maintained over time. In this regard, sustained efficacy outcomes that exclude patients presenting a transient seizure frequency reduction and those interrupting treatment are more rigorous and informative measures of response.

TABLE 2 Adverse events with brivaracetam treatment

Patients with adverse events	
N[a]	844
n (%)	254 (30.1)
Most frequently reported adverse events [reported by ≥1% of patients]	
N[a]	819
Somnolence, *n* (%)	55 (6.7)
Nervousness and/or agitation, *n* (%)	47 (5.7)
Vertigo, *n* (%)	28 (3.4)
Fatigue, *n* (%)	26 (3.2)
Headache, *n* (%)	21 (2.6)
Aggressiveness, *n* (%)	20 (2.4)
Mood change, *n* (%)	18 (2.2)
Dizziness, *n* (%)	19 (2.3)
Sleep disturbances, *n* (%)	15 (1.8)
Memory disturbance, *n* (%)	13 (1.6)
Nausea/vomiting, *n* (%)	8 (1.0)

Note: Adverse events reported by <1% of patients: stomach pain, tremor (both $n = 7$, .9%), disturbances in attention/concentration ($n = 6$, .7%), diplopia/blurred vision ($n = 5$, .6%), weight increase ($n = 4$, .5%), anxiety, hair loss, skin disorders (all $n = 3$, .4%), fever, hyporexia, pharyngodynia (all $n = 2$, .2%), abdominal pain, confusion, constipation, psychosis, tics, urinary disturbances, weight decrease (all $n = 1$, .1%).

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

So far, only limited evidence exists about the long-term sustained seizure frequency improvement with BRV treatment. A similar approach has been utilized to examine the time course of add-on BRV efficacy and assess sustained ≥50% and 100% response in three RCTs with a 12-week treatment period.[8,9] In the pooled efficacy population of 1160 patients, the 100% sustained response rates on Day 1 of treatment were 5.1% and 4.0% for BRV 100 and 200 mg/day and remained substantially unchanged by Day 84.[8] Sustained ≥50% responder status was achieved on Day 1 by 15.5%, 18.1%, and 19.4% of patients taking BRV at 50, 100, and 200 mg/day, and corresponding values on Day 84 were 34.8%, 35.8%, and 35.2%.[9] In a longitudinal, multicenter study, the 50% or greater seizure reduction at 12 months was observed in 33.1% of 262 included patients, including 10.9% reporting seizure freedom.[10]

The findings from the current study and pooled post hoc analysis of RCTs support the suggestion that BRV can have an early, sustained onset of action and a subset of responders may benefit from the first day of treatment, with potential utility when rapid onset of action is necessary. The favorable tolerability profile with initiation at target dose with no need for titration and the fast penetration of BRV into the brain may be reasons for the early onset of efficacy. Of note, the proportion of patients reaching sustained seizure control also increased over time; although the shorter duration of follow-up for later responders needs to be considered, this may suggest that efficacy can be sustained even in patients who respond later.

There is little evidence on how ASMs should be trialed, and most recommendations to tailor rational polypharmacy are empirical.[11] Data from literature suggest that favorable combinations usually consist of ASMs with different mechanisms of action.[11] Whereas additive or supra-additive efficacy has been observed with LEV and SCBs, including carbamazepine, oxcarbazepine, and lacosamide,[11] no evidence is available indicating how to favorably combine BRV. In this regard, the higher rates of SSF and SSR observed when BRV was added to SCBs suggest a potential enhancement of the effect on seizure control when these drug classes are coadministered that deserves to be further investigated alongside tolerability and pharmacokinetic issues before drawing definitive conclusions.

Adjunctive BRV was efficacious in reducing seizure frequency irrespective of LEV status, and the rates of SSF and SSR were higher among patients who had never been treated with LEV than patients who had a history of LEV use. These findings are consistent with the already available evidence from randomized controlled trials and real-world studies and suggest that a history of LEV treatment does not preclude the prescription of BRV.[4,12] Differences in characteristics of patients may have contributed to explaining differences in treatment efficacy across LEV subgroups, patients with a history

of LEV being likely to be affected by a more difficult to treat and severe epilepsy.

The higher rates of SSF and SSR observed in elderly patients also agree with prior evidence describing the greater effectiveness of BRV in older versus younger patients.[13–15] Notably, when studies report outcomes by age class, ASMs generally are found to be more efficacious in elderly than younger patients, and differences in outcomes across the age groups can largely be attributed to differences in characteristics of participants.[16,17]

BRV was discontinued by approximately 25% of the patients, and this figure substantially overlapped with the rates found in retrospective noninterventional studies[14,18–20]; the lack of efficacy was the main reason for drug withdrawal as expected according to the characteristics of the patients and study inclusion criteria. AEs were reported by one quarter of the population and had generally mild to moderate severity, and somnolence, headache, dizziness, and fatigue were the most frequent. These findings reinforced the overall favorable tolerability profile of add-on BRV treatment already demonstrated in prior randomized and nonrandomized studies.[14,18–22]

This study offers novel insights into the long-term response to add-on BRV from a novel, still neglected clinical perspective. Major strengths include the multicenter recruitment and large sample size, SSF and SSR as metrics of treatment efficacy, and the exploratory analysis by concomitant use of SCBs. In addition, the real-world setting can address the gap left by RCTs, which are typically characterized by restrictive inclusion criteria, rigid titration schemes, little or no dosing flexibility, and short duration, and offers higher external validity. Some limits also need to be considered, including the retrospective nature, unavailability of data outcome by seizure subtypes, and lack of standardized questionnaires to report AEs. As modifications in ASMs administered concomitantly to BRV have not been consistently reported, the influence of any changes in the therapeutic regimen remained unexplored. Furthermore, the open-label and uncontrolled design prevents any comparison between BRV and other ASMs.

5 | CONCLUSIONS

Adjunctive BRV was associated with sustained seizure frequency reduction in a subset of patients with focal seizures uncontrolled by concomitant ASMs. Seizure freedom is a clinically meaningful outcome, which plays a role in guiding selection and modification of therapeutic regimens. Importantly, how long seizure freedom is maintained is a key factor. The accurate reporting of rate and duration of seizure freedom in epilepsy studies across the spectrum of ASMs is warranted to provide more informed treatment decisions in clinical practice.

ACKNOWLEDGMENT

Open Access Funding provided by Universita Politecnica delle Marche within the CRUI-CARE Agreement. [Correction added on 17 May 2022, after first online publication: CRUI funding statement has been added.]

CONFLICT OF INTEREST

S.L. has received speaker's or consultancy fees from Angelini, Eisai, GW Pharmaceuticals, and UCB Pharma and has served on advisory boards for Angelini, Arvelle Therapeutics, Bial, and GW Pharmaceuticals. L.C. has received a consultancy fee from Eisai. M.P.C. has received speaker's or consultancy fees from Bial, Eisai, Italfarmaco, Sanofi, and UCB Pharma. S.C. has participated in pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, and Lusofarmaco. V.C. has received speaker's or consultancy fees from Eisai and UCB Pharma. G.D.G. has participated in advisory boards and pharmaceutical industry-sponsored symposia for Eisai, UCB Pharma, Bial, Lusofarmaco, LivaNova, and Arvelle Therapeutics. A.L.N. has received speaker's or consultancy fees from Eisai, Mylan, Bial, Sanofi, and UCB Pharma. P.P. has received consulting fees or speaker honoraria from UCB Pharma and Eisai. F.R. has received speaker's fees from Eisai, UCB, and LivaNova. E.R. has received fees for participation on advisory boards or scientific consultation from Eisai, GW Pharmaceuticals, Bial, and UCB Pharma. L.T. has received speaker's or consultancy fees from Arvelle Therapeutics, Eisai, and UCB Pharma. C.D.B. has received consulting fees or speaker honoraria by UCB Pharma, Eisai, GW Pharmaceuticals, Bial, and Lusopharma. None of the other authors has any conflict of interest to disclose. 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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REFERENCES

1. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Brivaracetam add-on for refractory focal epilepsy: a systematic review and meta-analysis. Neurology. 2016;86:1344–52.
2. Lattanzi S, Canafoglia L, Canevini MP, Casciato S, Chiesa V, Dainese F, et al. Adjunctive brivaracetam in focal epilepsy: real-world evidence from the BRIVAracetam add-on First Italian netwoRk STudy (BRIVAFIRST). CNS Drugs. 2021;35:1289–301.
3. Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
4. Lattanzi S, De Maria G, Rosati E, Didato G, Chiesa V, Ranzato F, et al. Brivaracetam as add-on treatment in focal epilepsy: a real-world time-based analysis. Epilepsia. 2021;62:e1–6.
5. Lattanzi S, Cagnetti C, Foschi N, Provinciali L, Silvestrini M. Eslicarbazepine acetate as adjunctive treatment in partial-onset epilepsy. Acta Neurol Scand. 2018;137:29–32.
6. Halford JJ, Edwards JC. Seizure freedom as an outcome in epilepsy treatment clinical trials. Acta Neurol Scand. 2020;142:91–107.
7. Gazzola DM, Balcer LJ, French JA. Seizure-free outcome in randomized add-on trials of the new antiepileptic drugs. Epilepsia. 2007;48:1303–7.
8. Klein P, Laloyaux C, Elmoufti S, Gasalla T, Martin MS. Time course of 75%-100% efficacy response of adjunctive brivaracetam. Acta Neurol Scand. 2020;142:175–80.
9. Klein P, Johnson ME, Schiemann J, Whitesides J. Time to onset of sustained 50% responder status in patients with focal (partial-onset) seizures in three phase III studies of adjunctive brivaracetam treatment. Epilepsia. 2017;58:e21–5.
10. Strzelczyk A, Zaveta C, von Podewils F, Möddel G, Langenbruch L, Kovac S, et al. Long-term efficacy, tolerability, and retention of brivaracetam in epilepsy treatment: a longitudinal multicenter study with up to 5 years of follow-up. Epilepsia. 2021;62:2994–3004.
11. Verrotti A, Lattanzi S, Brigo F, et al. Pharmacodynamic interactions of antiepileptic drugs: from bench to clinical practice. Epilepsy Behav. 2020;104(Pt A):106939.
12. Asadi-Pooya AA, Sperling MR, Chung S, Klein P, Diaz A, Elmoufti S, et al. Efficacy and tolerability of adjunctive brivaracetam in patients with prior antiepileptic drug exposure: a post-hoc study. Epilepsy Res. 2017;131:70–5.
13. Brodie MJ, Whitesides J, Schiemann J, D'Souza J, Johnson ME. Tolerability, safety, and efficacy of adjunctive brivaracetam for focal seizures in older patients: a pooled analysis from three phase III studies. Epilepsy Res. 2016;127:114–8.
14. Villanueva V, López-González FJ, Mauri JA, Rodriguez-Uranga J, Olivé-Gadea M, Montoya J, et al. BRIVA-LIFE study group. BRIVA-LIFE-A multicenter retrospective study of the long-term use of brivaracetam in clinical practice. Acta Neurol Scand. 2019;139:360–8.
15. Lattanzi S, Canafoglia L, Canevini MP, Casciato S, Cerulli Irelli E, Chiesa V, et al. Adjunctive brivaracetam in older patients with focal seizures: evidence from the BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST). Drugs Aging. Forthcoming 2022.
16. Lawthom C, Bermejo P, Campos D, McMurray R, Villanueva V. Effectiveness and safety/tolerability of eslicarbazepine acetate in epilepsy patients aged ≥60 versus <60 years: a subanalysis from the Euro-Esli Study. Neurol Ther. 2019;8:491–504.
17. Lattanzi S, Cagnetti C, Foschi N, Ciuffini R, Osanni E, Chiesa V, et al. Adjunctive perampanel in older patients with epilepsy: a multicenter study of clinical practice. Drugs Aging. 2021;38:603–10.
18. Steinhoff BJ, Christensen J, Doherty CP, Majoie M, De Backer M, Hellot S, et al. Effectiveness and tolerability of adjunctive brivaracetam in patients with focal seizures: second interim analysis of 6-month data from a prospective observational study in Europe. Epilepsy Res. 2020;165:106329.
19. Adewusi J, Burness C, Ellawela S, Emsley H, Hughes R, Lawthom C, et al. Brivaracetam efficacy and tolerability in clinical practice: a UK-based retrospective multicenter service evaluation. Epilepsy Behav. 2020;106:106967.
20. Steinig I, von Podewils F, Möddel G, Bauer S, Klein KM, Paule E, et al. Postmarketing experience with brivaracetam in the treatment of epilepsies: a multicenter cohort study from Germany. Epilepsia. 2017;58:1208–16.
21. Ben-Menachem E, Mameniškienė R, Quarato PP, Klein P, Gamage J, Schiemann J, et al. Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies. Neurology. 2016;87:314–23.
22. Steinhoff BJ, Bacher M, Bucurenciu I, Hillenbrand B, Intravooth T, Kornmeier R, et al. Real-life experience with brivaracetam in 101 patients with difficult-to-treat epilepsy—a monocenter survey. Seizure. 2017;48:11–4.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Lattanzi S, Ascoli M, Canafoglia L, Paola Canevini M, Casciato S, Cerulli Irelli E, et al; BRIVAFIRST Group. Sustained seizure freedom with adjunctive brivaracetam in patients with focal onset seizures. Epilepsia. 2022;63:e42–e50. https://doi.org/10.1111/epi.17223

APPENDIX 1

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