Long-term efficacy, tolerability, and retention of brivaracetam in epilepsy treatment: A longitudinal multicenter study with up to 5 years of follow-up

Adam Strzelczyk\textsuperscript{1,2} | Clara Zaveta\textsuperscript{1,2} | Felix von Podewils\textsuperscript{3} | Gabriel Möddel\textsuperscript{4} | Lisa Langenbruch\textsuperscript{4} | Stjepana Kovac\textsuperscript{4} | Catrin Mann\textsuperscript{1,2} | Laurent M. Willems\textsuperscript{1,2} | Juliane Schulz\textsuperscript{3} | Barbara Fiedler\textsuperscript{5} | Gerhard Kurlemann\textsuperscript{5,6} | Susanne Schubert-Bast\textsuperscript{1,2,7} | Felix Rosenow\textsuperscript{1,2} | Isabelle Beuchat\textsuperscript{1,2}

\textsuperscript{1}Epilepsy Center Frankfurt Rhine-Main and Department of Neurology, Goethe University Frankfurt, Frankfurt am Main, Germany
\textsuperscript{2}LOEWE Center for Personalized Translational Epilepsy Research (CePTER), Goethe University Frankfurt, Frankfurt am Main, Germany
\textsuperscript{3}Epilepsy Center Greifswald and Department of Neurology, University Medicine Greifswald, Greifswald, Germany
\textsuperscript{4}Epilepsy Center Münster-Osnabrück, Department of Neurology With Institute of Translational Neurology, University of Münster, Münster, Germany
\textsuperscript{5}Department of Neuropediatrics, University of Münster, Münster, Germany
\textsuperscript{6}St. Bonifatius Hospital, Lingen, Germany
\textsuperscript{7}Department of Neuropediatrics, Goethe University Frankfurt, Frankfurt am Main, Germany

Correspondence
Adam Strzelczyk, Epilepsy Center Frankfurt Rhine-Main, Center of Neurology and Neurosurgery, Goethe-University Frankfurt, Schleusenweg 2-16, 60528 Frankfurt am Main, Germany.

Abstract

Objective: This study was undertaken to evaluate the long-term efficacy, retention, and tolerability of add-on brivaracetam (BRV) in clinical practice.

Methods: A multicenter, retrospective cohort study recruited all patients who initiated BRV between February and November 2016, with observation until February 2021.

Results: Long-term data for 262 patients (mean age = 40 years, range = 5–81 years, 129 men) were analyzed, including 227 (87%) diagnosed with focal epilepsy, 19 (7%) with genetic generalized epilepsy, and 16 (6%) with other or unclassified epilepsy syndromes. Only 26 (10%) patients had never received levetiracetam (LEV), whereas 133 (50.8%) were switched from LEV. The length of BRV exposure ranged from 1 day to 5 years, with a median retention time of 1.6 years, resulting in a total BRV exposure time of 6829 months (569 years). The retention rate was 61.1% at 12 months, with a reported efficacy of 33.1% (79/239; 50% responder rate, 23 patients lost-to-follow-up), including 10.9% reported as seizure-free. The retention rate for the entire study period was 50.8%, and at last follow-up, 133 patients were receiving BRV at a mean dose of 222 ± 104 mg (median = 200, range = 25–400), including 52 (39.1%) who exceeded the recommended upper dose of 200 mg. Fewer concomitant antiseizure medications and switching from LEV to BRV correlated with better short-term responses, but no investigated parameters correlated with positive long-term outcomes. BRV was discontinued in 63 (24%) patients due to insufficient efficacy, in 29 (11%) for psychobehavioral adverse events, in 25 (10%) for other adverse events, and in 24 (9%) for other reasons.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. Epilepsia published by Wiley Periodicals LLC on behalf of International League Against Epilepsy
1 | INTRODUCTION

Antiseizure medications (ASMs) are typically used in a chronic manner, potentially as components of life-long treatment; therefore, ASM safety, tolerability, and efficacy must be maintained over time. Up to 30% of epilepsy patients are refractory to medical treatment, and a refractory disease course has been associated with increased morbidity and mortality, social stigma, reduced employment opportunities, and impaired quality of life for both patients with epilepsy and their caregivers. Therefore, the development of new and safe therapeutic options with sustained long-term efficacy remains urgently necessary.

Brivaracetam (BRV) is a high-affinity synaptic vesicle protein 2A ligand that exceeds the binding potential of levetiracetam (LEV) by 10- to 30-fold. BRV was approved in 2016 in Europe as an add-on therapy for the treatment of focal seizures in patients aged ≥4 years and was approved in the USA as an adjunctive or monotherapy for the treatment of focal seizures in patients aged ≥4 years (oral formulation only; an intravenous formulation has also been approved for patients aged ≥16 years).

In early randomized controlled trials (RCTs), BRV demonstrated good efficacy for the reduction of focal onset seizures and was associated with a favorable safety profile. Later, an open-label, long-term follow-up trial in adult patients with focal epilepsy reported good clinical efficacy (50% responder rate at 12 months) associated with a good safety profile for add-on BRV (doses up to 200 mg), with 50% of patients remaining in the trial at 4 years and 12.4% remaining at 9 years. A pooled analysis, including data from Phase IIb, Phase III, and long-term follow-up studies in adults with focal epilepsy, showed that adjunctive BRV was effective and well tolerated. However, results from clinical trials are difficult to extrapolate to real-life conditions due to the application of strict inclusion and exclusion criteria, the lack of dosing flexibility, and short follow-up periods that do not necessarily represent the realities of clinical practice. The results from previous real-life BRV studies are promising, suggesting potential efficacy beyond the treatment of focal seizures, including patients with generalized epilepsy, status epilepticus, or epileptic encephalopathies. Levetiracetam treatment failure should not preclude brivaracetam introduction. No long-term efficacy predictors could be identified.

Significance: BRV showed a clinically useful 50% responder rate of 33% at 12 months and overall retention of >50%, despite 90% of included patients having previous LEV exposure. BRV was well tolerated; however, psychobehavioral adverse events occurred in one out of 10 patients. Although we identified short-term response and retention predictors, we could not identify significant predictors for long-term outcomes.

Key Points
- Long-term postmarketing data for brivaracetam in 262 patients showed an overall retention rate of 50.8%
- At 12 months, the 50% responder rate for brivaracetam was 33.1%, with 10.9% reporting seizure freedom
- Previous treatment with levetiracetam (90%) did not impact brivaracetam retention or efficacy
- Levetiracetam treatment failure should not preclude brivaracetam introduction
- No long-term efficacy predictors could be identified

2 | MATERIALS AND METHODS

2.1 | Study settings and design

This retrospective, multicenter study was performed at university hospitals in Frankfurt am Main, Greifswald, and Münster, in Germany. The study received ethics committee approval; as this was a retrospective study, informed consent was not obtained.
consent was not required. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were closely followed.26 This study was not sponsored or funded by any commercial entity.

All epilepsy patients who were started on BRV between February 15, 2016, and November 15, 2016 were included in this analysis. Outcome data between 3 months and 1 year, as of February 2017, were previously published by Steinig et al.22 All patients who were exposed to at least one dose of BRV were included in the final analysis. The present study reports follow-up data that were collected through February 2021. The use of BRV in patients with status epilepticus has been reported separately.27 Epilepsy diagnoses were based on the latest definitions proposed by the International League Against Epilepsy and the International Bureau for Epilepsy.28,29 Information regarding epilepsy syndrome; seizure semiology; seizure etiology; patient demographics; current and previous ASM use, including a detailed history of LEV use; and comorbidities, including the modified Rankin Scale30 and the Charlson Comorbidity Index score, was provided by the treating physician at each study site.31 Using a standardized reporting form, the starting, maintenance, and maximum doses of BRV, length of BRV exposure, and BRV withdrawal rates were recorded. Patients were interviewed regarding the occurrence of treatment-emergent adverse events (TEAEs) at each clinic visit, and TEAEs were documented according to established World Health Organization criteria. Patients were typically seen every 3–6 months, and seizure frequency was obtained from medical notes and seizure diaries. Responder rates of 25%, 50%, and 75% were defined as reductions in seizure frequencies of ≥25% but <50%, ≥50% but <75%, and ≥75%, respectively, during follow-up compared with the 3-month baseline. No response was defined as a <25% change in seizure frequency. Seizure increase was defined as a >25% increase in seizure frequency. Responder rates are provided for the first 12 months of treatment and for the final 6 months of treatment. Retention rates are provided for the first 12 months of treatment and for the entire study period. Short-term predictors of response after 3 months have previously been reported.22

2.2 Data entry and statistical analysis

Statistical analyses were performed using SPSS Statistics, version 27.0 (IBM). Retention time on BRV was estimated using Kaplan–Meier survival curves, and the log-rank test was used to conduct comparisons between subgroups. Correlations among categorical variables were evaluated using the Wilcoxon signed-rank test. Binary variables were analyzed using the chi-squared or Fisher exact test, and continuous variables were assessed by t-test. The Benjamini–Hochberg (BH) procedure was applied to control for false discovery rate, using a p-value of .05.

3 RESULTS

3.1 Patients’ characteristics at baseline

We report on 262 patients, with a median follow-up of 1.6 years (range = 1 day to 5 years) and a total BRV exposure time of 569 years. The patients’ characteristics have previously been published by Steinig et al. covering the first year of BRV use in Germany as of February 201722 and are summarized in Table 1. Patients were taking a mean of 2.4 ± .9 ASMs (median = 2, range = 1–6 ASMs) before starting BRV, including 26 (10%) patients taking strong enzyme inducers and 163 (62.2%) patients taking a sodium channel blocker. Patients were exposed to a mean of 4.4 ± 3.8 additional ASMs (median = 4, range = 0–17) prior to the study, without including current ASMs. Only 26 (10%) patients had never been treated with LEV, and 133 (50.8%) were switched to BRV from a mean LEV dose of 2397 ± 1008 mg (median = 2250, range = 500–4000).

3.2 Treatment with BRV

Treatment with BRV in patients not using LEV at the study onset (n = 129) was introduced at a mean dose of 55.8 ± 27.7 mg (median = 50 mg, range = 10–200 mg), with a mean target dose of 128.1 ± 49.2 mg (median = 100 mg, range = 50–200) that was typically achieved within a median of 7 days. In those who were switched from LEV to BRV (n = 133), the initial mean BRV dose was 125.2 ± 77.9 mg (median = 100, range = 25–400), with a mean target dose of 175.7 ± 60.0 mg (median = 200, range = 50–400). The LEV to BRV switch was performed at a median ratio of 15:1 (mean = 14.8:1, range = 2:1 to 40:1). The maximal mean BRV dose was 214.8 ± 91.9 mg (median = 200, range = 50–400), with 88 patients (33.6%) exceeding the upper recommended dose of 200 mg. At last follow-up, 133 patients were receiving BRV at a mean dose of 222.0 ± 103.6 mg (median = 200, range = 25–400), with 52 patients (39.1%) exceeding the upper recommended dose of 200 mg.

3.3 Seizure outcomes during the first year of treatment

After 12 months of BRV treatment, responder rates were available for 160 patients, 79 patients had discontinued
BRV, and 23 patients were lost to follow-up. A 50% response rate (50% or greater seizure reduction) was reported by 79 patients (33.1%, 79/239), including 26 patients reporting seizure freedom (10.9%, 20 becoming and six remaining seizure-free as compared to baseline). An additional 15 (6.3%) patients had between 25% and <50% reductions in seizures. In 58 (24.3%) patients, no change in seizure frequency was reported, and eight (3.3%) patients reported increased seizure frequencies (Figure 1A).

We then compared the patients with >25% seizure reductions with those who reported either no clinical response, BRV discontinuation, or seizure increase or were lost to follow-up. A total of 125 (47.7%) patients showed >25% seizure reductions during the first 3 months of follow-up, and 94 (35.9%) patients presented with >25% seizure reduction after 12 months. During the short-term follow-up period (3 months), the use of fewer concomitant ASMs (1 vs. 2 or more) and switch from LEV were significantly associated with a better clinical response (hazard ratio [HR] = 1.46, 95% confidence interval [CI] = 1.12–1.90 and HR = 1.36, 95% CI = 1.05–1.76, respectively).22 During the long-term follow-up period (12 months), none of the investigated parameters was significantly correlated with long-term outcomes (Table 2).

### 3.4 | Terminal seizure outcomes during the last 6 months of follow-up

Terminal seizure outcome data for the last 6 months was available for 200 patients, whereas 55 (21.0%) patients discontinued BRV treatment before 6 months and seven (2.7%) were lost to follow-up. Overall, 51 patients reported seizure freedom (51/200, 25.5%), an additional 31 (15.5%) patients reported 75%–99% seizure reductions, 29 (14.5%) patients reported 50%–74% seizure reductions, and 11 (5.5%) patients reported 25%–49% seizure reductions. No changes were reported by 61 (30.5%) patients, and 17 (8.5%) patients described increases in seizure frequency (Figure 1B).

A >25% seizure reduction was reported by 122 (46.6%) patients. Age, sex, epilepsy syndrome, epilepsy etiology, epilepsy duration, seizure frequency, seizure semiology, the transition from LEV, maximal BRV dose, and the number of ASMs used at the time of BRV introduction were not significantly correlated with seizure outcomes. Prior therapy with LEV was associated with worse clinical response (response rate = 44.2% vs. 69.2%, p = .021, with significance lost after BH correction for multiple comparisons). The number of previously failed ASMs (dichotomized as 1–3 vs. >3) was significantly lower in patients with >25% seizure reduction (response rate = 53.9% vs. 40.0%, p = .034, with significance lost after BH correction).

### Table 1 | Clinical characteristics of the studied population (N = 262)

| Clinical characteristic | Value |
|-------------------------|-------|
| Age, mean ± SD*         | 40.0 ± 16.0 |
| Age range, n (%)        |       |
| <18 years               | 9 (3.4) |
| 18–40 years             | 128 (48.9) |
| 41–64 years             | 109 (41.6) |
| >65 years               | 16 (6.1) |
| Sex, female, n (%)      | 133 (50.8) |
| mRS, median (range)a    | 1 (1–6) |
| CCI, median (range)b    | 0 (0–4) |
| Epilepsy syndrome, n (%)|       |
| Idiopathic generalized epilepsy | 19 (7) |
| Symptomatic or cryptogenic focal epilepsy | 227 (87) |
| Symptomatic generalized epilepsy | 8 (3) |
| Unknown epilepsy syndrome | 8 (3) |
| Etiology, n (%)         |       |
| Cerebrovascular         | 21 (8.0) |
| Dysplasia/hippocampal sclerosis | 46 (17.6) |
| Tumor                   | 17 (6.5) |
| Other symptomatic causes | 60 (22.9) |
| Idiopathic/cryptogenic  | 106 (40.5) |
| Not available           | 12 (4.6) |
| Age at epilepsy onset, mean ± SD/median (range)b | 18.4 ± 17.6/14 (.1–80) |
| Epilepsy duration, mean ± SD/median (range)b | 21.6 ± 14.7/20 (.1–71) |
| Number of ASMs, mean ± SD/median (range)b | 2.4 ± 9.2/1 (1–6) |
| 1, n (%)                | 45 (17.2) |
| 2 or more, n (%)        | 217 (82.8) |
| Previously failed ASMs, mean ± SD/median (range)c,d | 4.4 ± 3.8/4 (0–17) |
| 0–3, n (%)              | 128 (48.9) |
| 4 or more, n (%)        | 130 (49.6) |
| Seizure frequency per month in the 3-month baseline period, mean ± SD/median (range) |       |
| Overall seizure frequency | 25.0 ± 47.9/7 (0–405) |
| GTCS, n = 113           | 4.4 ± 7.8/1.5 (.3–60) |

Abbreviations: ASM, antiseizure medication; CCI, Charlson Comorbidity Index; GTCS, generalized tonic–clonic seizures; mRS, modified Rankin Scale.

*aAt brivaracetam start.

*bSeven patients with missing data.

*cFour patients with missing data.

*dCurrent ASMs not included.
3.5 Retention and discontinuation of BRV

The median BRV retention time was 1.6 years (range = 1 day to 5 years), resulting in a total BRV exposure time of 6829 months (569 years). The probability of remaining on BRV was 61.1% (160/262 patients, 23 were lost to follow-up) after 12 months. The retention time was defined as the probability of remaining on BRV treatment and was assessed using Kaplan–Meier survival curves for all patients (Figure 2A), depending on the switch from LEV to BRV (Figure 2B), the number of previously failed ASMs (Figure 2C), and the number of concomitant ASMs used at the time of BRV initiation (Figure 2D). The retention rate did not differ significantly between groups stratified according to LEV to BRV switch (log-rank \(p = .31\)), the number of previously failed ASMs (log-rank \(p = .88\)), or the number of concomitant ASMs at BRV initiation (log-rank \(p = .54\)).

At the last follow-up, BRV was discontinued in 129 (49.2%) patients, resulting in an overall retention rate of 50.8% for the entire study period. BRV was discontinued due to insufficient efficacy in 63 (24.0%) patients, psychiatric adverse events in 29 (11.1%, 10 of these were switched from LEV due to psychobehavioral adverse events) patients, other adverse events in 25 (9.5%) patients, and other reasons in 24 (9.1%) patients. The reasons given for BRV discontinuation (not mutually exclusive) are summarized in Table 3.

4 DISCUSSION

Our study reflects 5 years of real-world experience with BRV in a large cohort of 262 patients who were started within the first 9 months after BRV became available on the market in Germany.
studies tend to focus on patients with focal epilepsy using fixed BRV dose regimens. By contrast, our study included patients of all ages and included those with generalized epilepsy.

Efficacy did not differ according to seizure semiology or epilepsy syndrome. Previous reports have suggested that BRV could be effective for treating generalized epilepsy, with good responses especially demonstrated in
patients with juvenile myoclonic epilepsies.\textsuperscript{23,37} However, the number of reported patients treated with BRV for generalized epilepsy remains very low, and additional studies focusing on this population remain necessary. In addition, the number of elderly patients with epilepsy is increasing, and data concerning this population, which is often excluded from RCTs, are also necessary.\textsuperscript{38} BRV showed a significant reduction in efficacy among older adults (>65 years) in the present study; however, significance was lost after correction for multiple comparisons. By contrast, post hoc analyses of Phase III studies suggested that BRV might represent a promising treatment for older adults.\textsuperscript{39}

A previous short-term study investigating the same population described in the present study at the 3-month follow-up time point reported that switch from LEV was associated with reduced BRV efficacy,\textsuperscript{22} whereas in this long-term follow-up study, neither previous treatment with LEV nor switch from LEV was associated with changes in BRV efficacy or retention. Previous data suggest that BRV is effective and well tolerated in patients switched from LEV.\textsuperscript{40,41} The reduced efficacy observed after 3 months in patients switched from LEV might be due to the BRV target dose being initiated almost immediately in those with previous LEV treatment, whereas those patients who were not switched from LEV were introduced to BRV using a slow titration period. Nonresponders might also be distinguished earlier among patients who switch from LEV compared with those without previous LEV treatment. Interestingly, a post hoc analysis of pooled data from RCTs reported a lower efficacy not only in LEV-exposed patients but also in patients treated with carbamazepine, topiramate, and lamotrigine.\textsuperscript{42}

These results suggest that previous ASM exposure is associated with BRV failure, regardless of their underlying mechanisms of action. In our cohort, the use of fewer concomitant ASMs and BRV initiation in patients not currently taking LEV were associated with better outcomes after 3 months.\textsuperscript{22} This is not surprising, as clinical practice shows that the chance of success is always higher in patients who get their first, second or third ASM. However, we were unable to identify predictors of long-term efficacy and cannot provide strong guidance for clinicians to assist in the determination of which patients will benefit from BRV use.
The retention rate was 61.1% after 12 months, with an overall retention rate of 50.8%. One systematic review that compared BRV retention rates in open-label extension studies with retention rates for other ASMs reported similar findings. The 52-week retention rate for BRV was 69.8%, whereas the retention rates for other ASMs at the same time point (eslicarbazepine, gabapentin, lacosamide, LEV, oxcarbazepine, perampanel, pregabalin, topiramate, and zonisamide) ranged between 63.3% and 66.7%.

One study investigating BRV prescriptions in a real-world setting reported a slightly higher 12-month retention rate (70.4%) than that found in this study. This discrepancy could be due to differences in the patients’ baseline characteristics and the study design. As previously described, the BRV retention rate appears to decline gradually over the first year (79.4% at 3 months, 75.8% at 6 months, and 61.1% at 12 months), followed by a relative stabilization period after 12 months. Initial efficacy, often referred to as the honeymoon period, is a well-known phenomenon, especially among patients with drug-resistant epilepsy. A similar finding was observed by our group, with a 41.2% responder rate (including 14.9% reporting seizure freedom) at 3 months, but only a 33.1% responder rate (including 10.9% reporting seizure freedom) at 12 months. Our results emphasize that BRV is associated with a good retention rate (similar to other ASMs), even among a population that includes >90% of patients with a history of LEV treatment. The retention rate did not differ between the groups stratified according to prior LEV treatment, the number of failed ASMs, or the number of concomitant ASMs, further supporting that LEV failure should not preclude BRV introduction.

During this long-term follow-up study, BRV was generally found to be safe and well tolerated. The most commonly reported adverse events were somnolence, dizziness, and psychobehavioral side effects, similar to those described in previous trials. The mechanism driving the psychobehavioral side effects of BRV remain unclear, although BRV activity on neurotransmitter systems, such as the γ-aminobutyric acid and serotonergic systems, has been postulated. Unlike LEV, BRV does not have α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonistic activity, which has been hypothesized as a contributing mechanism for the psychobehavioral adverse events observed in patients treated with LEV and could explain why transitioning from LEV to BRV can improve psychobehavioral symptoms in some patients. BRV was discontinued due to adverse events in 20.6% of our patients, which is a higher proportion than described in the previous literature and may be due to the real-world setting of our study, which was not limited by strict, a priori patient selection. When compared with other ASMs that are prescribed in a similar setting, BRV appeared equally or less disabling (discontinuation due to adverse events: 30% for zonisamide, 46% for pregabalin, and 19% for LEV). As previously reported, the lack of efficacy was the most commonly reported reason for BRV treatment discontinuation.

Several limitations of this study should be acknowledged. First, this study is limited by the risks inherent to any study with a retrospective design, including the potential for relevant information to be missing from records, the lack....

### Table 3: Reasons for brivaracetam discontinuation (n = 129)

| Reason                                | n  | %   |
|---------------------------------------|----|-----|
| Insufficient efficacy                 | 63 | 48.8|
| Psychobehavioral                      | 29 | 22.5|
| Depression                            | 6  |     |
| Irritability                          | 5  |     |
| Psychotic symptoms                    | 2  |     |
| Anxiety                               | 1  |     |
| Suicidal ideation                     | 1  |     |
| Unspecified                           | 14 | 10.9|
| CNS-related                           | 25 | 19.4|
| Confusion                             | 2  |     |
| Somnolence                            | 8  |     |
| Dizziness                             | 8  |     |
| Sleep disorders                       | 2  |     |
| Walking difficulty                    | 3  |     |
| Ataxia                                | 1  |     |
| Word-finding difficulties             | 1  |     |
| Others                                | 14 | 10.9|
| Nausea                                | 3  |     |
| Loss of appetite                      | 2  |     |
| GI problems                           | 7  | 5.5 |
| Pain                                  | 2  |     |
| Allergic reaction                     | 1  |     |
| Other reasons                         | 24 | 18.6|
| Unknown                               | 7  |     |
| Cost/medication access issues         | 5  |     |
| PNES                                  | 1  |     |
| Death or palliative care              | 3  |     |
| Child planning                        | 1  |     |
| Treatment adaptation                  | 6  |     |
| Pregnancy                             | 2  |     |

Abbreviations: CNS, central nervous system; GI, gastrointestinal; PNES, psychogenic nonepileptic seizures; TEAE, treatment-related adverse event.

*Insomnia and nightmares.

*Five cases of diarrhea and two cases of constipation.

*Phenytoin intoxication, seizure-free, treatment simplification.
of randomization, and variations in follow-up timing. The lack of a control group prevents the drawing of conclusions regarding BRV efficacy relative to other ASMs. BRV doses were not standardized in the present study, and 39.1% of patients exceeded the recommended dose of 200 mg. However, this real-world setting, which involved the up titration of BRV doses at the treating clinician’s discretion, represents one of the strengths of our study, as it reflects real-life clinical practices. Furthermore, BRV doses were not associated with retention or efficacy, suggesting that bias associated with BRV use beyond the recommended dose is unlikely. In addition, only few children were included, so that detailed information cannot be provided for the pediatric publication; later performed studies have answered this question.51 Further prospective studies, including the evaluation of scales measuring quality of life and psychosocial inventories, are warranted to fully evaluate the long-term efficacy and tolerability of BRV.

5 | CONCLUSIONS

This study confirms that add-on BRV was well tolerated in a real-world setting and improved long-term seizure control in patients with various epilepsy syndromes. The observed responder rates within the first 12 months of BRV therapy in this study were in line with those reported by prior RCTs, and the overall high retention rate of 50.8% underlined the good efficacy and tolerability of BRV. These findings were observed in a cohort in which 90% of patients had previous LEV exposure, suggesting that LEV treatment failure should not preclude BRV introduction.

ACKNOWLEDGMENT

Open access funding enabled and organized by ProjektDEAL.

CONFLICT OF INTEREST

A.S. reports personal fees and grants from Arvelle Therapeutics, Desitin Arzneimittel, Eisai, GW Pharmaceuticals companies, Marinus Pharma, UCB Pharma, UNEEG medical, and Zogenix. F.V.P. reports industry-funded travel with the support of Desitin Arzneimittel, Bial, Eisai Pharma, Arvelle Therapeutics, GW Pharmaceuticals, and UCB Pharma; and honoraria obtained for speaking engagements from Desitin Arzneimittel Zogenix, Bial, Arvelle Therapeutics, GW Pharmaceuticals, and UCB Pharma, and as part of a speaker’s bureau for Bial, Eisai Pharma, Arvelle Therapeutics, GW Pharmaceuticals, and UCB Pharma. G.M. reports industry-funded travel support from Desitin Arzneimittel, Eisai Pharma, and UCB Pharma, as well as speaking honoraria from UCB Pharma. L.L. reports honoraria for lecturing from Eisai, Biogen, and GW Pharmaceuticals. S.K. reports grants from Biogen and a grant from Deutsche Forschungsgemeinschaft. C.M. reports speaking honoraria from Eisai. L.M.W. reports travel support from Eisai. G.K. has obtained honoraria for speaking engagements from Desitin Arzneimittel, Eisai, UCB Pharma, Takeda, Shire, Zogenix, Neuraxpharm, Stada, and GW Pharmaceuticals. S.S.-B. reports personal fees from UCB, Desitin Pharma, and Shire. F.R. reports personal fees from Eisai, Medtronic, Cerbomed, ViroPharma, Sandoz, BayerVital, and Shire; grants and personal fees from UCB and Desitin Arzneimittel; personal fees and other from Novartis; and grants from the European Union and Deutsche Forschungsgemeinschaft. I.B. received a Postdoctoral Mobility Fellowship from the Swiss National Science Foundation. 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.

ORCID

Adam Strzelczyk ⓒ https://orcid.org/0000-0001-6288-9915
Lisa Langenbruch ⓒ https://orcid.org/0000-0001-9745-7258
Catrin Mann ⓒ https://orcid.org/0000-0001-6663-2631
Laurent M. Willems ⓒ https://orcid.org/0000-0001-8226-1674
Susanne Schubert-Bast ⓒ https://orcid.org/0000-0003-1545-7364
Felix Rosenow ⓒ https://orcid.org/0000-0002-3989-7471
Isabelle Beuchat ⓒ https://orcid.org/0000-0002-9300-4443

REFERENCES

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;3(342):314–9.
2. Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med. 2011;365(10):919–26.
3. Smeets VM, van Lierop BA, Vanhoutvin JP, Aldenkamp AP, Nijhuis FJ. Epilepsy and employment: literature review. Epilepsy Behav. 2007;10(3):354–62.
4. Strzelczyk A, Reese JP, Dodel R, Hamer HM. Cost of epilepsy. Pharmacoeconomics. 2008;26(6):463–76.
5. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. Lancet Neurol. 2011;10(11):961–8.
6. Jacoby A, Lane S, Marson A, Baker GA. Relationship of clinical and quality of life trajectories following the onset of seizures: findings from the UK MESS Study. Epilepsia. 2011;52(5):965–74.
7. Strzelczyk A, Klein KM, Willems LM, Rosenow F, Bauer S. Brivaracetam in the treatment of focal and idiopathic generalized epilepsies and of status epilepticus. Expert Rev Clin Pharmacol. 2016;9(5):637–45.
8. Dupuis N, Matagne A, Staelens L, Dournaud P, Desnous B, Gressens P, et al. Anti-ictogenic and antiepileptogenic
properties of brivaracetam in mature and immature rats. Epilepsia. 2015;56(5):800–5.

9. Wood MD, Gillard M. Evidence for a differential interaction of brivaracetam and levetiracetam with the synaptic vesicle 2A protein. Epilepsia. 2017;58(2):255–62.

10. Matagne A, Margineanu DG, Kenda B, Michel P, Klitgaard H. Anti-convulsive and anti-epileptic properties of brivaracetam (ucb 34714), a high-affinity ligand for the synaptic vesicle protein, SV2A. Br J Pharmacol. 2008;154(8):1662–71.

11. Niespodziany I, Andre VM, Leclere N, Hanon E, Ghisdal P, Wolff C. Brivaracetam differentially affects voltage-gated sodium currents without impairing sustained repetitive firing in neurons. CNS Neurosci Ther. 2015;21(3):241–51.

12. Yang X, Bognar J Jr, He T, Mohammed M, Niespodziany I, Andre VM, Leclere N, Hanon E, Ghisdal P, Wolff C, et al. Brivaracetam augments short-term depression and slow vesicle recycling. Epilepsia. 2015;56(12):1899–909.

13. BRIVIACT HIGHLIGHTS OF PRESCRIBING INFORMATION. UCB Pharma, SA, Brussels, Belgium. Briviact (brivaracetam).

14. Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Klein P, Schieman J, Sperling MR, Whitesides J, Liang W, O'Brien TJ, Borghs S, He QJ, Schulz AL, Yates S, Biton V. Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: an up to 11-year, open-label, follow-up trial. Epilepsia. 2020;61(4):636–46.

15. Toledo M, Whitesides J, Schiemann J, Johnson ME, Eckhardt K, McDonough B, et al. Safety, tolerability, and seizure control during long-term treatment with adjunctive brivaracetam for partial-onset seizures. Epilepsia. 2016;57(7):1139–51.

16. Steinhoff BJ, Staack AM, Hillenbrand BC. Randomized controlled antiepileptic drug trials miss almost all patients with ongoing seizures. Epilepsy Behav. 2017;66:45–8.

17. Walker MC, Sander JW. Difficulties in extrapolating from clinical trial data to clinical practice: the case of antiepileptic drugs. Neurology. 1997;49(2):333–7.

18. Steini G, 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(7):1208–16.

19. Strzelczyk A, Kay L, Bauer S, Immisch I, Klein KM, Knake S, et al. Use of brivaracetam in genetic generalized epilepsies and for acute, intravenous treatment of absence status epilepticus. Epilepsia. 2018;59(8):1549–56.
elderly: a systematic review and meta-analysis. Epilepsia. 2019;60(7):1325–40.
40. 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.
41. Yates SL, Fakhoury T, Liang W, Eckhardt K, Borghs S, D’Souza J. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. Epilepsy Behav. 2015;52:165–8.
42. 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.
43. Toledo M, Beale R, Evans JS, Steeves S, Elmoufti S, Townsend R, et al. Long-term retention rates for antiepileptic drugs: a review of long-term extension studies and comparison with brivaracetam. Epilepsy Res. 2017;138:53–61.
44. Novy J, Bartolini E, Bell GS, Duncan JS, Sander JW. Long-term retention of lacosamide in a large cohort of people with medically refractory epilepsy: a single centre evaluation. Epilepsy Res. 2013;106(1-2):250–6.
45. Nass RD, Kurth C, Kull A, Graf W, Kasper B, Hamer HM, et al. Adjunctive retigabine in refractory focal epilepsy: postmarketing experience at four tertiary epilepsy care centers in Germany. Epilepsy Behav. 2016;56:54–8.
46. Chung S, Wang N, Hank N. Comparative retention rates and long-term tolerability of new antiepileptic drugs. Seizure. 2007;16(4):296–304.
47. Löscher W, Poulter MO, Padjen AL. Major targets and mechanisms of antiepileptic drugs and major reasons for failure. Adv Neurol. 2006;97:417–27.
48. Gillard M, Fuks B, Leclercq K, Matagne A. Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties. Eur J Pharmacol. 2011;664(16):36–44.
49. Hansen CC, Ljung H, Brodtkor B, Reimers A. Mechanisms underlying aggressive behavior induced by antiepileptic drugs: focus on topiramate, levetiracetam, and perampanel. Behav Neurol. 2018;2018:2064027.
50. Brandt C, Klein P, Badalamenti V, Gasalla T, Whitesides J. Safety and tolerability of adjunctive brivaracetam in epilepsy: in-depth pooled analysis. Epilepsy Behav. 2020;103:106864.
51. Schubert-Bast S, Willems LM, Kurellmann G, Knake S, Muller-Schlüter K, Rosenow F, et al. Postmarketing experience with brivaracetam in the treatment of focal epilepsy in children and adolescents. Epilepsy Behav. 2018;89:89–93.

How to cite this article: 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. https://doi.org/10.1111/epi.17087