FULL-LENGTH ORIGINAL RESEARCH

A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures

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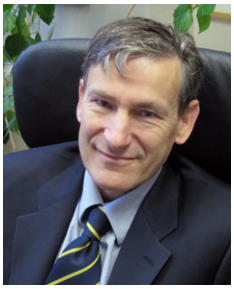

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Summary

Objective: **Brivaracetam (BRV), a selective and high-affinity synaptic vesicle protein 2A ligand, is in development as adjunctive treatment for partial-onset (focal) seizures (POS). This phase 3 study (N01358; NCT01261325) aimed to confirm the efficacy and safety/tolerability of BRV in adults (≥16–80 years) with POS.**

Methods: **This randomized, double-blind, placebo-controlled, multicenter study enrolled patients with uncontrolled POS despite ongoing treatment with 1–2 antiepileptic drugs. Patients exposed to levetiracetam ≤90 days before visit 1 were excluded. Patients entered an 8-week prospective baseline period, followed by a 12-week treatment period when they were randomized 1:1:1 to placebo (PBO), BRV 100 mg/day, or BRV 200 mg/day, started without up-titration. The co-primary efficacy outcomes were percent reduction over placebo in 28-day adjusted POS frequency, and ≥50% responder rate based on percent reduction in POS frequency from baseline to the treatment period.**

Results: **Seven hundred sixty-eight patients were randomized; 760 were included in the efficacy analysis: 259, 252, and 249 in PBO, BRV 100 mg/day, and BRV 200 mg/day groups, respectively. Percent reduction over PBO in 28-day adjusted seizure frequency (95% confidence interval [CI]) was 22.8% for BRV 100 mg/day (13.3–31.2%; $p < 0.001$) and 23.2% for BRV 200 mg/day (13.8–31.6%; $p < 0.001$). The ≥50% responder rate (odds ratio vs. PBO; 95% CI) was 21.6% for PBO, 38.9% for BRV 100 mg/day (2.39; 1.6–3.6; $p < 0.001$), and 37.8% for BRV 200 mg/day (2.19; 1.5–3.3; $p < 0.001$). Treatment-emergent adverse events (TEAEs) occurred in 155 (59.4%) of 261 PBO patients versus 340 (67.6%) of 503 BRV-treated patients (safety population). Discontinuation rates due to TEAEs were 3.8%, 8.3%, and 6.8% for PBO, BRV 100 mg/day, and BRV 200 mg/day, respectively. Most frequent TEAEs (PBO versus BRV) were somnolence (7.7% vs. 18.1%), dizziness (5.0% vs. 12.3%), and fatigue (3.8% vs. 9.5%).**

Significance: **Adjunctive BRV 100 and 200 mg/day was efficacious in reducing POS in adults without concomitant levetiracetam use and was well tolerated.**

KEY WORDS: **Brivaracetam, Focal epilepsy, Phase 3, Efficacy, Safety/tolerability, Partial-onset seizures.**

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Key Points

- One of the largest studies in epilepsy to date: a phase 3 study of adjunctive brivaracetam 100–200 mg/day in adults with uncontrolled partial-onset seizures without concomitant levetiracetam
- Brivaracetam was initiated at therapeutic dosage without uptitration
- Adjunctive brivaracetam 100 and 200 mg/day significantly reduced partial-onset seizure frequency over 12 weeks versus placebo
- Seizure reduction occurred in patients who had previously discontinued levetiracetam as well as in those who were levetiracetam naive
- Discontinuation due to TEAEs was low, and the proportion of patients who entered long-term follow-up was high (88.0%), suggesting that brivaracetam was generally well tolerated

Epilepsy affects almost 70 million people worldwide.[1] In approximately 35% of patients,[2,3] particularly those with focal epilepsy, it is uncontrolled by antiepileptic drug (AED) treatment. This proportion has changed little since the 1990s, despite the introduction of third-generation AEDs with various mechanisms of action,[3–5] highlighting an ongoing unmet need for more effective treatment.

One of the most widely used third-generation AEDs is levetiracetam (LEV), an S-enantiomer derivative of pyrrolidine acetamide. The antiseizure action of LEV is thought to be mediated by binding to synaptic vesicle protein 2A (SV2A) with subsequent modulation of neurotransmitter release into the synapse.[6] In animal models, the binding affinity of LEV analogues to SV2A correlates closely with antiseizure potency.[7] Brivaracetam (BRV) is a new, rationally designed SV2A ligand with high selectivity and approximately 20-fold higher binding affinity than LEV in both animal and human brain.[8] BRV has broad-spectrum antiseizure activities in models of focal and generalized epilepsy.[9] It induces more potent and complete suppression of seizures and kindling acquisition than LEV in animal models of epilepsy, and has a wide therapeutic index.[9]

To date, the BRV clinical development program has included two fixed-dose phase 3 studies in adults with uncontrolled focal epilepsy, with dosages ranging from 5 to 100 mg/day.[10,11] One study showed statistically significant seizure frequency reduction with adjunctive BRV 50 mg/day compared with placebo (PBO).[10] The other study did not meet its primary endpoint, which required statistical significance at the 50 mg/day dose, although statistical significance was achieved at 100 mg/day.[11] Subgroup analyses suggested that patients without concomitant LEV use (irrespective of any prior LEV exposure) may have a greater seizure frequency reduction than those taking LEV.[10,11] An additional placebo-controlled phase 3 study using flexible, individualized BRV doses provided evidence that BRV was well tolerated at dosages up to 150 mg/day.[12]

The objective of the current phase 3 study was to evaluate the efficacy, safety, and tolerability of BRV 100 or 200 mg/day as adjunctive therapy in adults with uncontrolled partial-onset (focal) seizures (POS) despite treatment with one or two concomitant AEDs. Based on the results of the previous phase 3 studies,[10,11] patients receiving concomitant LEV were excluded.

Methods

Study design

This was a phase 3, randomized, double-blind, PBO-controlled, multicenter, parallel-group, study (N01358; NCT01261325, ClinicalTrials.gov). Patients were enrolled from epilepsy centers in North America, Western Europe, Eastern Europe, Latin America, and Asia. The study comprised an 8-week prospective baseline period, 12-week treatment period, and a 4-week down-titration period followed by a 2-week drug-free period, or entry into a long-term follow-up study (N01379; NCT01339559).

The study was conducted in accordance with the International Conference on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by institutional review boards at all study sites, and written informed consent was obtained from all patients or their legal representatives before enrollment.

Participants

Eligible patients were aged ≥16–80 years, with well-characterized focal epilepsy or epileptic syndrome, uncontrolled with one or two concomitant AEDs at stable dosage for at least 1 month before visit 1 (3 months for phenobarbital, phenytoin, and primidone). Patients must have had an electroencephalography (EEG) reading compatible with the diagnosis of focal epilepsy within the last 5 years, and a brain magnetic resonance imaging/computed tomography (MRI/CT) scan within the last 2 years. They must have had ≥8 POSs during the 8-week baseline period, with ≥2 seizures during each 4-week interval, and ≥2 POSs, with or without secondary generalization, per month during the 3 months prior to visit 1. Inclusion of each patient was reviewed centrally by the sponsor's study physician using the subject eligibility confirmation form prior to randomization.

Patients taking concomitant LEV, or who had taken LEV within 90 days prior to visit 1, were excluded. Other exclusion criteria included nonmotor simple partial seizures as the only seizure type, cluster seizures, psychogenic

nonepileptic seizures, history of status epilepticus during the year preceding visit 1, rapidly progressing brain disorder or tumor, terminal illness, serious infection, or history of suicide attempt.

Randomization and masking

A 1:1:1 central randomization (random permuted blocks with a block size of three) stratified by country, LEV status (never used vs. prior use), and number of AEDs previously used or discontinued prior to study entry (≤2 vs. >2) was employed to ensure balance across treatment groups. Prior LEV use was defined as LEV discontinuation ≥90 days prior to visit 1.

The randomization schedule was produced by a biostatistician who was not otherwise involved in this study, and was maintained in a secure location until the data were unblinded for final analysis. Study drug kits were prepared according to the treatment sequence allocation defined in the randomization list. Patients were assigned to a treatment group at enrollment by an interactive voice/computer response system (IXRS), which was accessed by the investigator. All personnel who were involved with the study were blinded to the patients' treatment, except those directly responsible for packaging of study drug or management of the IXRS.

Procedures

During the treatment period, patients were treated with PBO, BRV 100 mg/day, or BRV 200 mg/day, administered in two equally divided doses per day, without up-titration. Oral film-coated tablets of BRV 10, 25, and 50 mg and matching PBO tablets were used; these tablet strengths were used both to help maintain the blinding (allowing all patients to take two tablets per dose throughout the treatment period) and to allow down-titration for those patients who did not enter the long-term follow-up study.

Outcomes

The co-primary efficacy outcomes were percent reduction over PBO in 28-day adjusted POS frequency during the treatment period, and ≥50% responder rate based on percent reduction in seizure frequency from baseline to the treatment period. Secondary efficacy outcomes included percent reduction in seizure frequency from baseline to the treatment period, categorized percent reduction from baseline in seizure frequency over the treatment period, and seizure freedom rate (all seizures). Blood samples were collected for measurement of BRV plasma concentration post-dose at weeks 2, 4, 8, and 12. Safety and tolerability outcomes included adverse events (AEs), laboratory tests, vital signs, and electrocardiography (ECG) recordings. Patients were asked at each study visit whether they had experienced any AEs, and they could also spontaneously report AEs at any time during the study.

Statistical analysis

Of the two co-primary efficacy outcomes, the ≥50% responder rate required the larger sample size. Sample size calculations identified that, for this outcome, 231 analyzable patients per treatment group were required to detect a 15% difference in responder rates between BRV and PBO at the 0.025 significance level (two-tailed) with 90% power, assuming responder rates of 20% and 35% for PBO and BRV, respectively. Based on this sample size, the power achieved for percent reduction over PBO in 28-day adjusted seizure frequency was 94%.

The efficacy analyses were based on the intention-to-treat (ITT) population, consisting of all randomized patients who received ≥1 dose of study drug and had ≥1 postbaseline seizure diary entry. The safety population consisted of all randomized patients who received ≥1 dose of study drug.

Percent reduction in seizure frequency over PBO was evaluated by analysis of covariance (ANCOVA) with log-transformed treatment period 28-day adjusted seizure frequency as the outcome. The ≥50% responder rate was assessed using a logistic regression model. Both co-primary outcome measures were analyzed using effects of treatment, country, and the four possible combinations of LEV status (never used or prior use) with number of previous AEDs (≤2 or >2), and log-transformed baseline seizure frequency as a continuous covariate. Statistical significance was evaluated using the Hochberg multiple comparison procedure. Prespecified descriptive subgroup analyses were also conducted based on LEV status, number of previous AEDs, and geographic region. Post hoc exploratory statistical analysis was performed for the LEV status subgroup data. Percent reduction in seizure frequency over PBO was evaluated by ANCOVA with log-transformed treatment period 28-day adjusted seizure frequency as the outcome, and ≥50% responder rate was assessed using a logistic regression model. Both analyses included an effect of treatment and used log-transformed baseline seizure frequency as a continuous covariate. A post hoc exploratory descriptive subgroup analysis was conducted based on reason for prior discontinuation of LEV (insufficient efficacy, AE).

For the secondary efficacy outcomes, percent reduction in seizure frequency from baseline to treatment period was analyzed using the Wilcoxon-Mann-Whitney test with Hodges–Lehmann nonparametric effect estimates and corresponding two-sided 95% confidence intervals (CIs). Categorized percent reduction from baseline in seizure frequency was compared using the Mantel-Haenszel test for the comparison of raw mean scores. Seizure freedom rates were compared using Fisher's exact test. Seizure freedom was defined as completion of the entire treatment period without reporting seizures of any type and without any missing seizure diary days.

Safety and tolerability outcomes were analyzed descriptively. AEs were coded according to the Medical Dictionary

for Regulatory Activities (MedDRA; Version 15.0). Recurrent AEs were counted only once.

Results

The study enrolled patients from December 2010 through December 2013. A total of 768 patients were randomized at 147 sites in 27 countries; 764 (99.5%) of these were included in the safety population (Fig. 1). The ITT population comprised 760 patients (99.0%). Overall, 696 (90.6%) of 768 patients completed the study. Discontinuation rates were 6.5% in the PBO group versus 11.4% for BRV 100 mg/day, and 10.4% for BRV 200 mg/day. Overall, 676 (88.0%) of 768 entered the long-term follow-up study.

Baseline demographics and epilepsy characteristics were similar across treatment groups (Table 1), except for gender (higher proportion of females in the BRV 100 mg/day group). The mean (standard deviation, SD) duration of epilepsy was 22.8 (13.7) years (ITT population). Almost half of patients (359/760, 47.2%) had previously failed ≥5 AEDs. The majority of patients were taking two concomitant AEDs at study entry (542/760, 71.3%).

Both co-primary outcomes were statistically significant ($p < 0.001$ vs. PBO) for both BRV dosages (Fig. 2). Percent reduction in 28-day adjusted seizure frequency over PBO (95% CI) was 22.8% (13.3–31.2) for BRV 100 mg/day and 23.2% (13.8–31.6) for BRV 200 mg/day. The ≥50% responder rate (odds ratio [95% CI]) was 21.6% for PBO, 38.9% (2.39 [1.6–3.6]) for BRV 100 mg/day, and 37.8% (2.19 [1.5–3.3]) for BRV 200 mg/day.

The secondary efficacy outcomes were also positive (Fig. 3). Median percent reduction in seizure frequency from baseline was 17.6% for PBO, 37.2% for BRV 100 mg/day ($p < 0.001$), and 35.6% for BRV 200 mg/day ($p < 0.001$). Median percent reduction in seizure frequency from baseline for simple POS (type IA) was 14.9%, 25.4%, and 31.5% for PBO, BRV 100 mg/day, and BRV 200 mg/day, respectively; for complex POS (type IB) median percent reduction in frequency was 21.4% (PBO), 39.3% (BRV 100 mg/day), and 41.5% (BRV 200 mg/day), and for POS evolving to secondary generalized seizures (type IC) it was 24.7% (PBO), 62.5% (BRV 100 mg/day), and 82.1% (BRV 200 mg/day) (Fig. S1). Because some patients reported multiple seizure types at baseline, Figure S1 includes each patient in every applicable category and consequently has a greater total patient number than Figure 3A. Categorized percent reduction in seizure frequency from baseline was statistically significant for BRV compared with PBO across the six predefined categories ($p < 0.001$ for both dosages; Fig. S2). In a predefined analysis, seizure freedom (all seizure types) during the treatment period was 2/259 (0.8%) for the PBO group, 13/252 (5.2%) for BRV 100 mg/day ($p = 0.003$), and 10/249 (4.0%) for BRV 200 mg/day ($p = 0.019$).

A total of 412 patients had previously tried and discontinued LEV due to insufficient efficacy (278, 67.5%), AEs (77, 18.7%), other reason (31, 7.5%), or unknown reason (26, 6.3%). Efficacy was demonstrated by both co-primary outcomes in the subgroups with previous LEV exposure and in LEV-naive patients in a post hoc statistical analysis, and appeared to be greater in the LEV-naive population (Fig. 4A,B). The treatment effect appeared to be greater in patients who previously discontinued LEV due to AEs than those who reported insufficient efficacy, although the

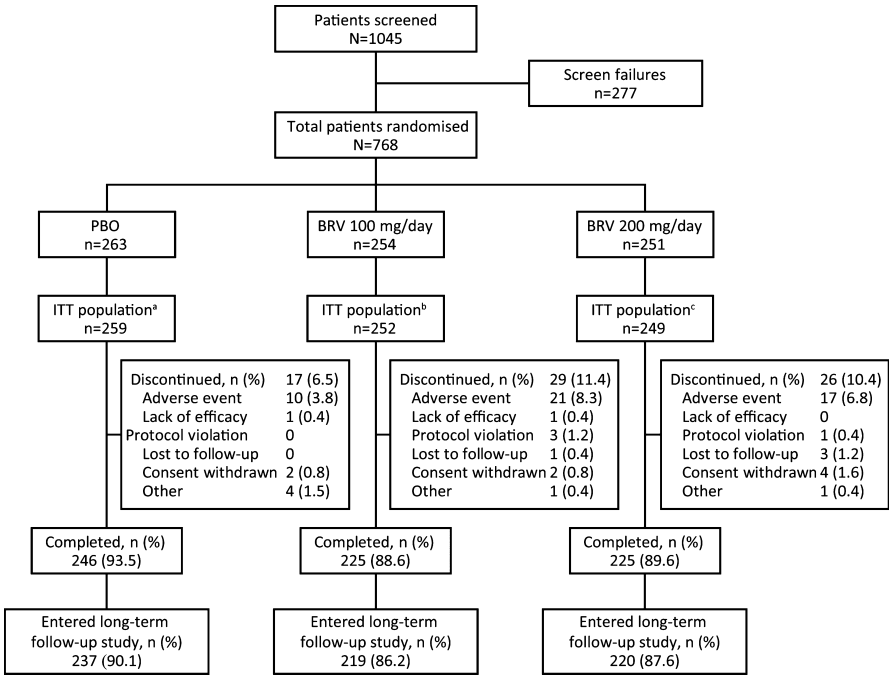

Figure 1.
Patient disposition. BRV, brivaracetam; ITT, intention-to-treat; PBO, placebo. [a]Patients excluded due to discontinuation for unspecified reasons prior to study drug administration (n = 2), discontinuation due to a TEAE (n = 1), and withdrawal of consent (n = 1). [b]Patients excluded due to discontinuation for unspecified reasons prior to study drug administration (n = 1), and discontinuation due to a TEAE (n = 1). [c]Patients excluded due to discontinuation for unspecified reasons prior to study drug administration (n = 1), and lost to follow-up (n = 1).
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Table 1. Patient demographics (safety population) and baseline epilepsy characteristics (ITT population)

Safety population	PBO (n = 261)	BRV 100 mg/day (n = 253)	BRV 200 mg/day (n = 250)
Age, years, mean (SD)	39.8 (12.5)	39.1 (13.4)	39.8 (12.8)
Gender, female, n (%)	128 (49.0)	151 (59.7)	117 (46.8)
Race, white, n (%)	189 (72.4)	182 (71.9)	182 (72.8)
Weight, kg, mean (SD)	76.1 (20.0)	74.1 (16.8)	75.4 (19.0)
BMI, kg/m^2, mean (SD)	26.7 (5.7)	26.7 (5.7)	26.4 (6.0)
Region, n (%)			
Europe (EU)	128 (49.0)	120 (47.4)	125 (50.0)
North America	62 (23.8)	65 (25.7)	61 (24.4)
Asia/Pacific/Other	32 (12.3)	31 (12.3)	28 (11.2)
Latin America	29 (11.1)	27 (10.7)	28 (11.2)
Europe (non-EU)	10 (3.8)	10 (4.0)	8 (3.2)
ITT population	**PBO (n = 259)**	**BRV 100 mg/day (n = 252)**	**BRV 200 mg/day (n = 249)**
Duration of epilepsy, years, mean (SD)	22.7 (13.3)	22.2 (13.3)	23.4 (14.6)
Age at first seizure, years, mean (SD)	17.5 (13.4)	17.4 (13.9)	16.8 (13.5)
Baseline POS frequency per 28 days, median (min, max)	10.0 (3, 560)	9.5 (2, 354)	9.3 (3, 710)
Number of prior AEDs, n (%)			
0–1	46 (17.8)	53 (21.0)	45 (18.1)
2–4	92 (35.5)	80 (31.7)	85 (34.1)
≥5	121 (46.7)	119 (47.2)	119 (47.8)
Number of concomitant AEDs, n (%)			
1	75 (29.0)	70 (27.8)	69 (27.7)
2	181 (69.9)	182 (72.2)	179 (71.9)
≥3	3 (1.2)	0	1 (0.4)
Concomitant AEDs[a]			
Carbamazepine	96 (37.1)	94 (37.3)	93 (37.3)
Lamotrigine	67 (25.9)	69 (27.4)	61 (24.5)
Valproate	60 (23.2)	58 (23.0)	48 (19.3)
Oxcarbazepine	32 (12.4)	38 (15.1)	50 (20.1)
Topiramate	48 (18.5)	38 (15.1)	28 (11.2)
Lacosamide	36 (13.9)	34 (13.5)	38 (15.3)
LEV status, n (%)			
Never used LEV	116 (44.8)	116 (46.0)	115 (46.2)
Prior LEV use	143 (55.2)	136 (54.0)	134 (53.8)

AEDs, antiepileptic drugs; BMI, body mass index; BRV, brivaracetam; ITT, intention-to-treat; LEV, levetiracetam; PBO, placebo; POS, partial-onset seizure; SD, standard deviation.

[a]Taken by >10% of patients in any treatment group.

number of patients in the discontinuation due to AEs subgroups was small (Fig. 4C,D). Efficacy was also seen in subgroups with both ≤2 and >2 previous AEDs (Fig. 4E,F).

Response to BRV 100 mg/day was seen across all regions (Fig. S3A,B). However, for BRV 200 mg/day, there appeared to be a higher response in North America, Latin America, Asia-Pacific/Other countries, and non-EU European countries than in EU countries. For ≥50% responder rate, the placebo response was highest in non-EU European countries and lowest in Asia-Pacific/Other countries.

Mean BRV plasma concentrations in the 200 mg/day group (2.02–2.06 μg/ml at weeks 2, 4, 8, and 12) were approximately twofold higher than in the 100 mg/day group (1.06–1.15 μg/ml).

Treatment-emergent AEs (TEAEs) were reported in 155 (59.4%) of 261 patients in the PBO group, 173 (68.4%) of 253 patients in the BRV 100 mg/day group, and 167 (66.8%) of 250 patients in the 200 mg/day group (Table 2). The most frequently reported TEAEs were somnolence, dizziness, and fatigue (Table 2). The incidence of irritability was low (0.4% PBO; 3.2% BRV 100 mg/day, 2.8% BRV 200 mg/day, and 3.0% BRV overall). TEAEs leading to discontinuation of study drug occurred in 3.8%, 8.3%, and 6.8% of patients treated with PBO, BRV 100 mg/day, and BRV 200 mg/day, respectively. Drug-related TEAEs were more common in the BRV groups than placebo (22.2% PBO; 38.3% BRV 100 mg/day; and 44.0% BRV 200 mg/day). The majority of TEAEs were mild or moderate in intensity.

Psychiatric TEAEs were infrequent, and included anxiety (1.1% PBO; 2.2% BRV overall), insomnia (1.1% PBO; 2.0% BRV overall), and depression (0.4% PBO; 0.8% BRV overall). The overall incidence of psychiatric TEAEs was similar for both BRV dosages (10.3% 100 mg/day and 11.2% 200 mg/day) versus PBO (7.7%). The incidence of suicidal ideation was low and equal for PBO (one patient,

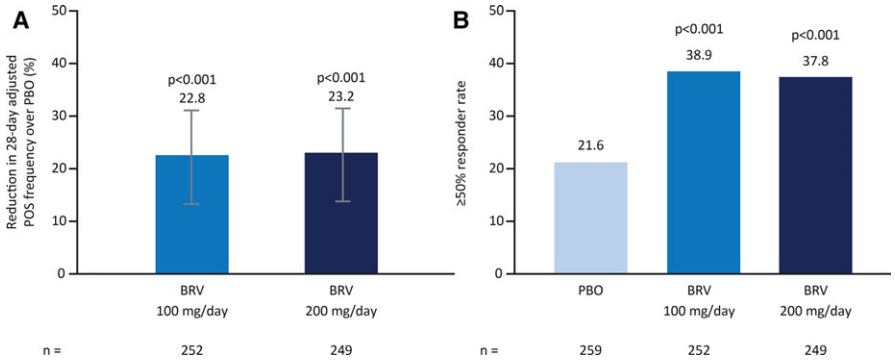

Figure 2.
Co-primary efficacy outcomes (ITT population). Percent reduction over placebo in 28-day adjusted partial-onset seizure frequency* during the treatment period (**A**); ≥50% responder rate for partial-onset seizure frequency from baseline to the end of treatment period (**B**). Error bars represent 95% confidence interval. BRV, brivaracetam; ITT, intention-to-treat; PBO, placebo; POS, partial-onset seizure. *Twenty-eight days adjusted POS frequency was calculated by dividing total number of POS by number of days for which diary was completed during the treatment period, and multiplying the resulting value by 28.

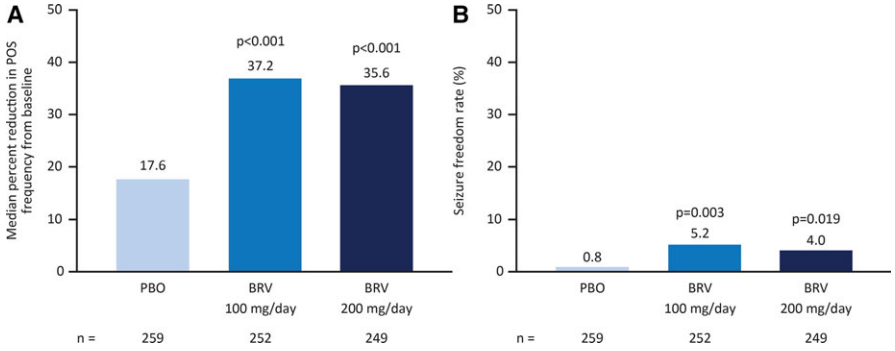

Figure 3.
Secondary efficacy outcomes (ITT population). Median percent reduction (95% confidence interval) in partial-onset seizure frequency from baseline (**A**); seizure freedom rate (all seizure types) during treatment period (**B**). BRV, brivaracetam; ITT, intention-to-treat; PBO, placebo; POS, partial-onset seizure.

0.4%) and BRV overall (two patients, 0.4%; one patient in each dose group). Two deaths were reported during the study, both in the BRV 200 mg/day group: one sudden unexplained death in epilepsy and one of unknown cause. Neither of these deaths was considered by the investigator to be related to BRV treatment. No clinically relevant differences between treatment groups were observed for any changes from baseline in vital signs, physical findings, hematology or blood chemistry parameters, or ECG findings.

Discussion

With 768 randomized patients, the present study is one of the largest interventional studies conducted to date in patients with epilepsy. Our data demonstrate that adjunctive BRV 100 and 200 mg/day had a robust, statistically significant effect for both co-primary efficacy outcomes: percent reduction in seizure frequency over PBO per 28 days and ≥50% responder rate. The positive results from the current study compare favorably with previous phase 3 fixed-dose studies of BRV, which included patients receiving concomitant LEV (limited to 20% of patients).[10,11] Secondary efficacy analyses also supported BRV efficacy for both the 100 and 200 mg/day dosages, including significantly higher seizure freedom rates (5.2% and 4.0%, respectively) versus PBO (0.8%). To our knowledge, this is the first study of an adjunctive AED to demonstrate a statistically significant effect on seizure freedom in adults for both dosages tested (a recent study of oxcarbazepine-XR[13] and a study of eslicarbazepine[14] reported statistically significant seizure freedom rates only for the highest dosages tested). However, the seizure freedom reported in the current study was observed over the 12-week treatment period and may not be replicated in long-term studies.

Our study had several novel design features. Firstly, in consideration of previous work suggesting that BRV may

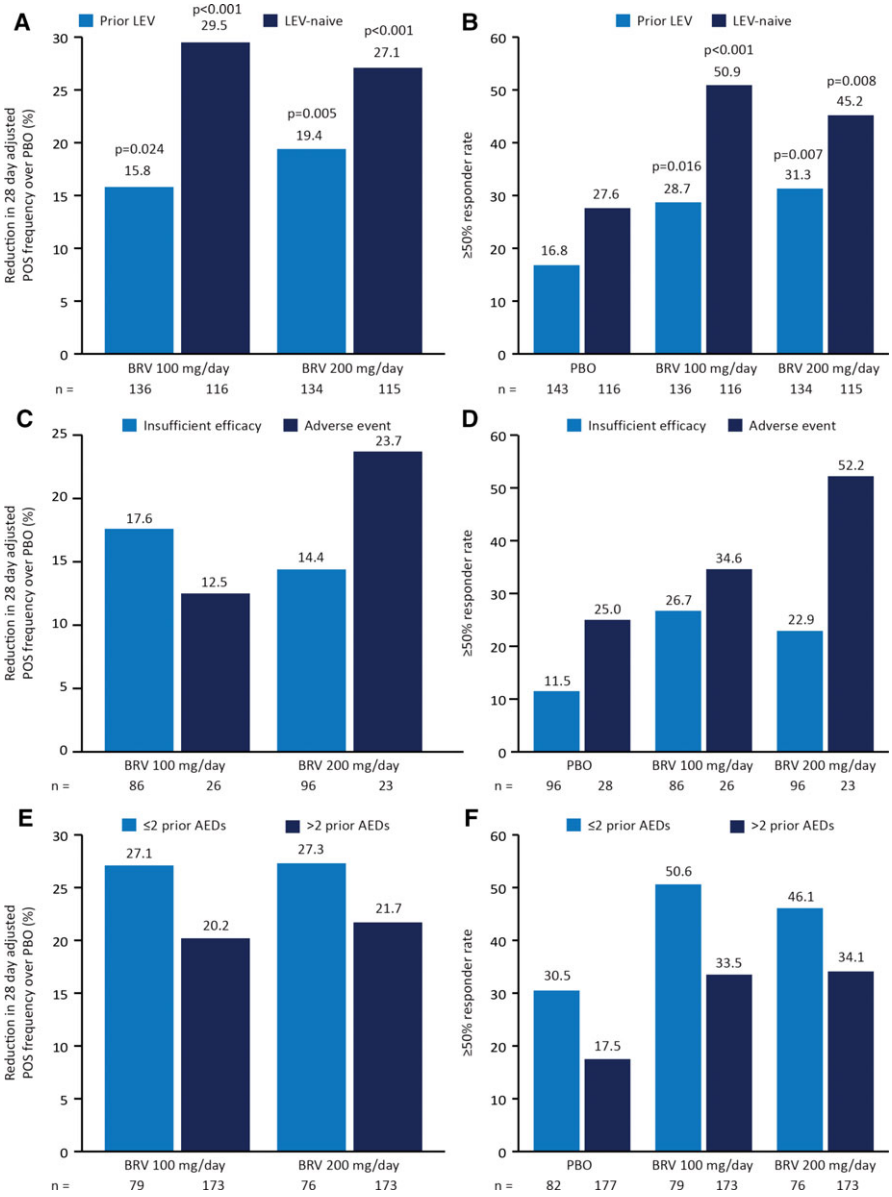

Figure 4.
Subgroup analysis (ITT population). Percent reduction over placebo in 28-day adjusted partial-onset seizure frequency during the treatment period in prior LEV and LEV-naive patients (**A**); ≥50% responder rate for partial-onset seizure frequency from baseline to the end of treatment period in prior LEV and LEV-naive patients (**B**); percent reduction over placebo in 28-day adjusted partial-onset seizure frequency during the treatment period according to reason for prior discontinuation of LEV* (**C**); ≥50% responder rate for partial-onset seizure frequency from baseline to the end of treatment period according to reason for prior discontinuation of LEV* (**D**); percent reduction over placebo in 28-day adjusted partial-onset seizure frequency during the treatment period according to number of prior AEDs (**E**); ≥50% responder rate for partial-onset seizure frequency from baseline to the end of treatment period according to number of prior AEDs (**F**). *Analysis by reason for prior discontinuation of LEV excluded one patient who was previously treated with either levetiracetam or pregabalin in a blinded study. AEDs, antiepileptic drugs; BRV, brivaracetam; ITT, intention-to-treat; LEV, levetiracetam; PBO, placebo; POS, partial-onset seizure.

have reduced efficacy in patients taking concomitant LEV,[10,11] patients taking concomitant LEV were excluded from the study and a predetermined subgroup analysis of efficacy by prior exposure to LEV was conducted. Both BRV and LEV are presumed to exert their antiseizure effect by binding to the SV2A protein and modulating neurotransmitter release into the synapse,[6,7,15–17] although details of how this translates into reduced seizure potential are as yet unknown. This approach to study design, namely making use of what is already known about the patient population and potential interactions with concomitant medications, could be considered in future epilepsy studies, in order to address the potential for "rational polypharmacy," that is, evaluation of AED combination therapy based on considerations of mechanism of action. This methodology could be extended by an analysis of efficacy by concomitant AED, to identify any AED combinations with the potential for particularly high or low efficacy, or any increased incidence of AEs, for particular seizure types or patient profiles. It is likely that a very large patient population would be needed for such an analysis to generate meaningful results. However, with increasing use of informatics in medicine, this approach may become more common in future clinical studies. Furthermore, the outcome of this study design, namely demonstration of efficacy of BRV among the subgroup of patients who had previously failed LEV, has direct clinical application. In addition, subject eligibility for each patient was reviewed centrally prior to randomization to ensure that they met all the inclusion criteria (i.e., they had focal epilepsy) and none of the exclusion criteria.

The results of the exploratory post hoc subgroup analysis by LEV exposure showed that statistically significant

Table 2. Summary of treatment-emergent adverse events (safety population)

Parameter, n (%)	PBO (n = 261)	BRV 100 mg/day (n = 253)	BRV 200 mg/day (n = 250)	Combined BRV (n = 503)
Any TEAE	155 (59.4)	173 (68.4)	167 (66.8)	340 (67.6)
TEAE leading to discontinuation of study drug	10 (3.8)	21 (8.3)	17 (6.8)	38 (7.6)
Drug-related TEAEs[a]	58 (22.2)	97 (38.3)	110 (44.0)	207 (41.2)
Nervous system disorders[b]	68 (26.1)	94 (37.2)	105 (42.0)	199 (39.6)
Psychiatric disorders[b]	20 (7.7)	26 (10.3)	28 (11.2)	54 (10.7)
Severe TEAE[a]	11 (4.2)	16 (6.3)	15 (6.0)	31 (6.2)
Serious TEAE[c]	9 (3.4)	8 (3.2)	8 (3.2)	16 (3.2)
Death	0	0	2 (0.8)	2 (0.4)
TEAEs reported by ≥5% of patients in any treatment group				
Somnolence	20 (7.7)	49 (19.4)	42 (16.8)	91 (18.1)
Dizziness	13 (5.0)	26 (10.3)	36 (14.4)	62 (12.3)
Fatigue	10 (3.8)	19 (7.5)	29 (11.6)	48 (9.5)
Headache	22 (8.4)	17 (6.7)	20 (8.0)	37 (7.4)
Urinary tract infection	8 (3.1)	13 (5.1)	2 (0.8)	15 (3.0)

BRV, brivaracetam; PBO, placebo; TEAE, treatment-emergent adverse event.
[a]As judged by the investigator.
[b]Classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0 primary system organ class.
[c]Serious TEAEs were defined as those that resulted in death, were life-threatening, required or prolonged hospitalization, resulted in persistent or significant disability or incapacity, or were important medical events, congenital anomalies, or birth defects.

($p < 0.05$ vs. PBO) seizure reduction occurred in both previously LEV-exposed and LEV-naive patients. Percent reductions in seizure frequency over PBO per 28 days and the ≥50% responder rates were higher across treatment groups for LEV-naive patients than for LEV-exposed patients. However, it is important to note that there was a response in patients with previous LEV exposure. This finding suggests the possibility that BRV may be an effective AED in some patients who have previously failed LEV, although these post hoc findings would need to be confirmed in further clinical trials. In addition, BRV reduced seizure frequency regardless of the number of prior AEDs.

A surprising finding in our study was the lack of a dose–response effect between the 100 and 200 mg/day dosages. Dose–response findings have been diverse in previous phase 2b and phase 3 studies of BRV. In two studies, a dose–response effect was observed for lower BRV dosages of 5, 20, and 50 mg/day, with only the 50 mg/day dose being effective in reducing seizure frequency.[10,18] These two studies both demonstrated a 22% reduction in seizure frequency over PBO for the 50 mg/day dosage, similar to that shown with the 100 and 200 mg/day dosages in the present study. However, two other previous studies found the 50 mg/day dosage ineffective.[11,19] Of interest, one of these two studies was positive at 100 mg/day,[11] whereas the other was negative at 150 mg/day.[19] There is, at present, no clear explanation for this diversity in the dose–response effect of BRV.

As in the previous phase 2b and phase 3 studies,[10–12,18,19] BRV appeared to be well tolerated, even at 200 mg/day. The overall safety and tolerability profile of BRV was consistent with that in the previous studies and similar between the two dosages, although some TEAEs, namely dizziness and fatigue, may be dose related. Discontinuation of BRV due to TEAEs was low—8.3% and 6.8% for the 100 and 200 mg/day dosages, respectively. This is similar to previous phase 3 studies for BRV dosages of 50–150 mg/day.[10–12] The relatively low overall discontinuation rate in the BRV groups (10.9%) may indicate that BRV has a wide therapeutic window, and suggests that the higher dose is well below the limit of tolerability. The TEAEs occurring with higher incidence in BRV- versus PBO-treated patients were central nervous system (CNS)-related: somnolence, dizziness and fatigue. They had a relatively low incidence (8–19%), again similar to findings of previous phase 2b and phase 3 studies.[10–12,18,19] This is notable given the initiation of BRV at full target dose, without up-titration. Titration of AEDs up to an effective dose is usually warranted because of known tolerability issues. However, previous BRV studies have demonstrated that it is well tolerated even when initiated at a therapeutic dose.[10,11] Psychiatric AEs were infrequent, also in line with previous phase 3 BRV studies.[10–12]

Potential limitations of the study include, similar to other phase 3 adjunctive AED trials, the short duration. The long-term effects of BRV will be evaluated in the open-label extension study. Sources of potential bias include self-recording of seizure frequency and seizure type data. Investigators may have been biased either for or against selection of patients who had previously failed LEV. Multiplicity of comparisons was compensated for by the Hochberg method.

In conclusion, this large phase 3 study demonstrates that adjunctive treatment with BRV 100 or 200 mg/day is

effective and generally well tolerated in adult patients with uncontrolled POS without concomitant LEV use, with low rates of discontinuation due to AEs. BRV also appeared to be effective in the subgroup of patients who had previously failed LEV.

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Author Contributions

PKl was an investigator, interpreted data, and contributed to writing the first draft. JS designed the study, interpreted data, and revised the report. MRS, CB, and PKw were investigators, interpreted data, and revised the report. JW interpreted data and contributed to writing the first draft. WL analyzed and interpreted data, and revised the report. TS designed the study, managed the study, interpreted data, contributed to writing the first draft, and revised the report.

Conflict of Interest

PKl reports personal fees from UCB Pharma during the conduct of the study; as well as personal fees from Eisai, Sunovion, and Marinus; and grant from Lundbeck. JS, JW, and WL are current employees of UCB Pharma. TS was an employee of UCB Pharma during the study and the development of the manuscript. WL owns UCB stocks. MRS reports grants from UCB Pharma, personal fees from UCB Pharma, during the conduct of the study; personal fees from Wiley, grants from Eisai, Sunovion, Marinus, UCB Pharma, SK Life Sciences, GlaxoSmithKline, Upsher Smith, Accoda, Medtronics, and Brain Sentinel, outside the submitted work. CB reports other fees from UCB Pharma, during the conduct of the study; grants and personal fees from Otsuka and UCB Pharma; personal fees from Eisai, Desitin, Pfizer, Novartis, and GlaxoSmithKline, outside the submitted work. PKw reports grants from UCB Pharma, during the conduct of the study; grants and personal fees from UCB Pharma, Eisai, and GlaxoSmithKline, outside of the submitted work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Median percent reduction in seizure frequency from baseline for simple partial-onset seizures (type IA), complex partial-onset seizures (type IB), and secondary generalized partial-onset seizures (type IC) (ITT population).

Figure S2. Secondary efficacy outcome (ITT population).

Figure S3. Subgroup analysis (ITT population).