Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: A phase III randomized, double-blind, placebo-controlled trial

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Epilepsia, 55(1):57–66, 2014
doi: 10.1111/epi.12433

SUMMARY

Purpose: Brivaracetam (BRV) is a novel high-affinity synaptic vesicle protein 2A ligand currently being investigated for the treatment of epilepsy. The purpose of this phase III study was to evaluate the efficacy and safety/tolerability of adjunctive BRV in adults with uncontrolled partial-onset (focal) seizures.

Methods: This was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose trial (N01253; NCT00464269). Adults aged 16–70 years with well-characterized partial epilepsy not fully controlled despite treatment with one or two antiepileptic drugs (AEDs) were enrolled. Patients who experienced eight or more partial-onset seizures, whether or not secondarily generalized, during the 8-week prospective baseline period were randomized (1:1:1:1) to receive twice-daily placebo (PBO) or BRV (5, 20, or 50 mg/day) without titration. The primary efficacy endpoint was percent reduction over PBO in baseline-adjusted partial-onset seizure frequency/week during the 12-week treatment period. Comparison of BRV with PBO was sequential (50, 20 mg/day, then 5 mg/day). Secondary endpoints included ≥50% responder rate and median percent reduction from baseline in partial-onset seizure frequency/week. Post hoc analyses included the primary efficacy endpoint evaluated over 28 days and exploratory subanalyses of efficacy by seizure subtype. Safety and tolerability assessments included treatment-emergent adverse events (TEAEs), laboratory tests, electrocardiography, vital signs, and physical and neurologic examinations.

Key Findings: Of 400 patients randomized, 396 were included in the intent-to-treat (ITT) population (PBO n = 98, BRV 5 mg/day n = 97, BRV 20 mg/day n = 100, BRV 50 mg/day n = 101) and 392 comprised the modified ITT (mITT) population. A total of 361 (91.2%) of 396 patients completed the study. Most patients (78.3%) were receiving two concomitant AEDs. Percent reduction in partial-onset seizure frequency/week over PBO was −0.9% (p = 0.885) for BRV 5 mg/day, 4.1% (p = 0.492) for BRV 20 mg/day, and 12.8% (p = 0.025) for BRV 50 mg/day (mITT population). Statistical significance was also achieved for the percent reduction over PBO in baseline-adjusted partial-onset seizure frequency/28 days for BRV 50 mg/day (22.0%; p = 0.004) but not for the other BRV dose groups. In the BRV 50 mg/day group, statistical significance was also seen for the ≥50% responder rate (BRV 32.7% vs. PBO 16.7%; p = 0.008) and median percent reduction from baseline in partial-onset seizure frequency/week (BRV 30.5% vs. PBO 17.8%; p = 0.003). In the exploratory subanalysis by seizure subtype, median percent reduction from baseline in seizure frequency/week and ≥50% responder rate were numerically greater than PBO in the BRV 20 and 50 mg/day groups for simple partial, complex partial, and secondarily generalized seizures. BRV was generally well tolerated, with the majority of TEAEs being mild-to-moderate in intensity. Of the TEAEs reported by ≥5% patients, those with a frequency ≥3% higher than PBO for any dose of BRV compared with PBO were somnolence, dizziness, fatigue, influenza, insomnia, nasopharyngitis, vomiting, diarrhea, urinary tract infection, and nausea.
Brivaracetam (BRV) is a pyrrolidine derivative currently being investigated for the treatment of epilepsy (Bialer et al., 2010). It is a novel high-affinity synaptic vesicle protein 2A (SV2A) ligand (Kenda et al., 2004; Gillard et al., 2011). Preclinical studies demonstrated efficacy in a wide range of animal models of partial-onset (focal) and generalized seizures (Matagne et al., 2008) and a higher affinity (>30-fold) for SV2A in human cerebral cortex compared with levetiracetam (LEV) (Gillard et al., 2011). Pharmacokinetic studies have indicated a bioavailability close to 100% and plasma protein binding of <20% (Rolan et al., 2004). The drug is completely and rapidly absorbed throughout the gastrointestinal tract, an effect that is not altered by food (Sargentini-Maier et al., 2007; Rolan et al., 2008).

Two dose-ranging phase IIb studies (N01193 and N01114) showed that BRV may be efficacious and well tolerated as adjunctive treatment in patients with partial-onset seizures and supported further clinical development (French et al., 2010; van Paasschen et al., 2013). Study N01193 met its primary endpoint, with BRV 50 mg/day demonstrating a statistically significant reduction in baseline-adjusted partial-onset seizure frequency/week over placebo (PBO) (French et al., 2010). In study N01114, although BRV 50 and 150 mg/day showed a numerically greater reduction than PBO in baseline-adjusted partial-onset seizure frequency, the study failed to show statistically significant differences between BRV 50 or 150 mg/day and PBO in the primary efficacy analysis (van Paasschen et al., 2013). In these studies, the incidence of the most common adverse events (AEs) (headache, somnolence, fatigue, nausea, nasopharyngitis, and dizziness) and the proportion of patients discontinuing due to AEs were similar for BRV and PBO (Brodsky et al., 2007; von Rosenstiel & Perucca, 2009).

Development of BRV in patients with epilepsy has continued with three phase III studies. Two were confirmatory, fixed-dose studies (N01252 [NCT00490035] and N01253 [NCT00464269]) in patients with partial epilepsy, and one a flexible-dose safety study (N01254 [NCT00504881]) in patients with partial or generalized epilepsy. Herein, we report the findings of one of these studies, a placebo-controlled fixed-dose study (N01253), which was designed to further evaluate the efficacy, safety/tolerability of BRV as an adjunctive treatment for uncontrolled partial-onset seizures in adults.

**Methods**

**Study design**

This was a phase III, prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, confirmatory trial (N01253; NCT00464269) conducted between September 2007 and January 2009. Patients were recruited from 85 sites in five countries: Australia, Brazil, Canada, Mexico, and the U.S.A. The study consisted of an 8-week prospective baseline period, followed by a 12-week treatment period, and either a 1-week downtitration period or entry into an optional open-label long-term follow-up study (N01199; NCT00150800). At the end of the baseline period patients were randomized in a 1:1:1:1 ratio to receive BRV (5, 20, or 50 mg/day) administered twice daily in equally divided doses without titration, or matching PBO. Treatment was assigned via an Interactive Voice Response System using a central randomization method (random permuted blocks) that stratified for concomitant LEV use at study entry (“yes” or “no”); patients and investigators were blinded to treatment. Each patient was assigned a visit box number corresponding to a centrally prepared visit box from where the patient collected their treatment. At the discretion of the investigator, one fallback option to the immediate lower dose level was allowed for all patients. Patients remained on their fallback dosage for the rest of the treatment period. At the end of the treatment period, patients either continued into the long-term follow-up study at a dosage of 50 mg/day (or 20 mg/day in case of fallback) or were downtitrated and entered a 2-week drug-free period (Fig. S1).

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 before enrollment.

**Study population**

Patients aged 16–70 years with well-characterized partial epilepsy (International League Against Epilepsy [ILAE] classification) (International League Against Epilepsy, 1989): two or more partial-onset seizures/month during the 3 months prior to screening and eight or more partial-onset seizures during the 8-week prospective baseline. Patients were uncontrolled on one to two concomitant antiepileptic drugs (AEDs) at optimal stable dosages for ≥1 month prior to screening and throughout the treatment period. Vagus nerve stimulation was allowed and was not counted as a concomitant AED. Benzodiazepines taken more than once/week for any indication were considered to be a concomitant AED. Concomitant LEV use was limited to 20% of all randomized patients.

The main exclusion criteria were nonmotor simple partial seizures as the only seizure type; a history or presence of seizures occurring only in clusters before randomization; a history or presence of either status epilepticus (during 1 year preceding screening or during baseline) or pseudo-seizures. Patients with a rapidly progressing brain disorder or brain tumor were excluded, as were patients with other serious uncontrolled disease.

**Efficacy assessments**

The primary efficacy variable was the partial-onset seizure frequency/week over the 12-week treatment period, with the percent reduction over PBO being the primary endpoint. Secondary efficacy variables included median percent reduction from baseline in partial-onset seizure frequency/week, ≥50% responder rate (the percentage of patients with a ≥50% reduction in partial-onset seizure frequency/week from baseline), and seizure freedom from all seizure types (the percentage of patients completing the treatment period without experiencing seizures of any type and having seizure daily record card data available for all days during the treatment period).

**Safety and tolerability assessments**

AEs were recorded and their severity (mild, moderate, or severe) and relationship to the study medication were assessed. AEs were categorized as serious (SAEs) if they were life-threatening, resulted in death, a persistent or significant disability, a congenital birth defect, or needed in-patient hospitalization. Centrally conducted laboratory tests (including blood chemistry, hematology, and urinalysis parameters) and physical and neurologic examination findings, vital signs, body weight, and electrocardiography (ECG) assessments carried out locally were also recorded.

**Statistical methods**

**Determination of sample size**

The sample size calculation was based on the primary efficacy variable. A total of 87 patients/arm were required to detect a treatment difference of −0.223 between BRV and PBO in the natural log-transformed partial-onset seizure frequency/week with 90% power, at a two-sided significance level of 0.050. The treatment difference of −0.223 on the log-transformed scale corresponded to a 20% reduction over PBO. Comparison of each BRV arm with PBO was performed according to a predefined sequential procedure, starting with the 50 mg/day group, followed by 20 mg/day, and finally 5 mg/day to maintain the overall type I error rate. To compensate for some loss of power in the 20 and 5 mg/day BRV groups due to the sequential testing procedure, 100 patients/arm were included in the study.

**Primary efficacy analysis**

The primary efficacy analysis was based on parametric analysis of covariance (ANCOVA) with log-transformed treatment period partial-onset seizure frequency adjusted over 7 days as the outcome, with effects for treatment and stratification factors (concomitant LEV use and geographic region). The log-transformed baseline partial-onset seizure frequency per week was used as a continuous covariate. Treatment effects were characterized using percent reduction over PBO after back-transformation of least squares means from the ANCOVA. Using the predefined sequential procedure (50, 20 mg/day, then 5 mg/day), a statistically significant outcome at the 0.050 significance level was required for BRV 50 mg/day over PBO.

A nonparametric ANCOVA was carried out to assess the robustness of the results of the parametric analysis. For each individual treatment group comparison, a regression of partial-onset seizure frequency during the treatment period versus the baseline period was performed. A Mantel–Haenszel test was then used to assess the difference in raw-mean scores.

A post hoc analysis was produced for partial-onset seizure frequency standardized to a 28-day duration, for comparison with the ANCOVA results based on the 7-day adjusted partial-onset seizure frequency. In addition, subanalyses for efficacy were carried out for simple partial, complex partial, and secondarily generalized seizure subtypes, and also for patients who were LEV-naive, had prior LEV use, and had concomitant LEV use.

Statistical comparisons for percent reduction from baseline in partial-onset seizure frequency/week were based on the Wilcoxon-Mann-Whitney test. Statistical comparisons for ≥50% responder rate were based on a logistic regression model, with an effect for treatment and log-transformed baseline partial-onset seizure frequency/week as a continuous covariate. Statistical comparisons for seizure freedom rates were performed using Fisher’s exact test. Statistical significance was reported at the 0.050 significance level.

Epilepsia, 55(1):57–66, 2014
doi: 10.1111/epi.12433
Populations analyzed

The intent-to-treat (ITT) population comprised all randomized patients who took ≥1 dose of BRV. The modified ITT (mITT) population was defined as all patients in the ITT population, with the exclusion of four patients (Fig. 1). All efficacy analyses were based on the mITT population, except for the nonparametric analysis of the primary efficacy variable, which was based on the ITT population. All safety analyses were based on the ITT population.

RESULTS

Patients

Of 509 patients screened, 400 were randomized. Four patients were excluded: one due to failure to take the study medication and three due to randomization errors. The remaining 396 patients (98, 97, 100, and 101 in PBO, BRV 5 mg/day, BRV 20 mg/day, and BRV 50 mg/day groups, respectively) comprised the ITT population. A further four patients were excluded from the ITT population; three (two receiving PBO, and one receiving BRV 20 mg/day) due to site noncompliance issues and one (BRV 5 mg/day) identified as a clinical outlier prior to unblinding. This patient had more than 100 seizures per day during the 12 weeks prior to study entry and during the study. In addition, this patient presented with extremely frequent eye blinking and ocular movements lasting only a few seconds, with or without an impairment of awareness, which was primarily suggestive of eyelid myoclonia with or without absences. Therefore, the remaining 392 patients were included in the mITT population (Fig. 1). Overall, 361 (91.2%) of 396 patients completed the study (268 [89.9%] BRV; 93 [94.9%] PBO), with 21 patients (5.3%) withdrawing because of AE(s) (19 [6.4%] BRV; two [2.0%] PBO) and an additional patient in the PBO group (0.3%) withdrawing because of lack of effi-

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Figure 1.

Patient disposition. aPatients excluded from efficacy analyses due to serious and persistent site noncompliance with applicable U.S. Food and Drug Administration (FDA) regulation, Good Clinical Practice, and International Conference on Harmonization guidelines. bPatient identified as a clinical outlier prior to study unblinding with >100 seizures per day during the 12 weeks prior to study entry and during the study. In addition, this patient’s clinical presentation consisted of extremely frequent eye blinking and ocular movements lasting only a few seconds, with or without an impairment of awareness, which was primarily suggestive of eyelid myoclonia with or without absences. cPercentages are based on the ITT population. dIncludes lost to follow-up, withdrawal of consent, and other reasons. ePatients who completed the 12-week treatment period. ITT, intent-to-treat.

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Epilepsia, 55(1):57–66, 2014
doi: 10.1111/epi.12433
The majority of patients (347/396, 87.6%) subsequently entered the long-term, open-label, follow-up study (261 [87.6%] BRV; 86 [87.8%] PBO).

Overall, the mean BRV dose was 4.7, 19.0, and 48.3 mg/day in the BRV 5 mg/day, BRV 20 mg/day, and BRV 50 mg/day groups (ITT population). Only 18 patients of a possible 396 used the fallback option: 3 (3.1%) in the PBO group compared with 4 (4.1%) in the BRV 5 mg/day group, 5 (5.0%) in the BRV 20 mg/day group, and 6 (5.9%) in the BRV 50 mg/day group.

Baseline demographics and epilepsy characteristics

Baseline demographic and epilepsy characteristics were well balanced across treatment groups (Table 1). Most patients in the ITT population (310/396, 78.3%) were taking two AEDs at baseline. In the 5 years prior to study entry, 248 (62.6%) of 396 patients had taken and discontinued at least two AEDs, and 66 (16.7%) of 396 had taken and discontinued at least five AEDs. Prior to study entry, 89 (22.5%) of 396 patients had previously taken LEV and discontinued it. During the baseline period, 395 (99.7%) of 396 patients experienced partial-onset seizures (predominantly complex partial seizures 335/396, 84.6%; simple partial seizures, 148/396, 37.4%; and secondarily generalized seizures 135/396, 34.1%); 13 (3.3%) of 396 patients experienced generalized seizures and 2 (0.5%) of 396 unclassifiable seizures. The median (Q1–Q3) baseline partial-onset seizure frequency/week was 2.6 (1.6–4.5), 2.4 (1.4–5.6), 2.2 (1.5–6.9), and 2.9 (1.5–7.2) in the PBO, BRV 5 mg/day, BRV 20 mg/day, and BRV 50 mg/day groups, respectively.

Efficacy

The median (Q1–Q3) partial-onset seizure frequency/week during the treatment period was 2.2 (1.4–4.2), 1.8 (1.0–5.6), 2.0 (1.1–5.5), and 1.7 (0.9–4.8), in the PBO, BRV 5, BRV 20, and BRV 50 mg/day groups, respectively.

Percent reduction over PBO in partial-onset seizure frequency/week

The percent reduction over PBO in partial-onset seizure frequency/week during the 12-week treatment period (primary efficacy variable) is shown in Table 2. The reduction observed in the BRV 50 mg/day group was statistically significant (p = 0.025) and was confirmed by the nonparametric sensitivity analysis at this dose level (p = 0.003). In the post hoc analysis evaluating the percent reduction in partial-
onset seizure frequency standardized to 28 days, the difference was statistically significant for BRV 50 mg/day (p = 0.004) (Table 2).

**Secondary efficacy analyses**

**Median percent reduction from baseline in partial-onset seizure frequency/week**

Over the 12-week treatment period, the median percent reduction from baseline in partial-onset seizure frequency/week was 17.8% for PBO compared with 20.0% for BRV 20 mg/day, and 30.5% for BRV 50 mg/day (Fig. 2A). The reduction was statistically significant in the 50 mg/day BRV group (p = 0.003).

**Responder rate of ≥50%**

Over the 12-week treatment period, the proportion of patients achieving a ≥50% reduction in the frequency of partial-onset seizures was 16 (16.7%) of 96 for PBO compared with 21 (21.9%) of 96 for BRV 5 mg/day, 23 (23.2%) of 99 for BRV 20 mg/day, and 33 (32.7%) of 101 for BRV 50 mg/day (Fig 2B). The ≥50% responder rate was statistically significant versus PBO in the BRV 50 mg/day group (p = 0.008).

**Seizure freedom (all seizure types)**

Seizure freedom during the entire 12-week treatment period was achieved in six patients in the BRV groups: none in the PBO group compared with one (1.1%) in the BRV 5 mg/day group, one (1.0%) in the BRV 20 mg/day group, and four (4.0%) in the BRV 50 mg/day group.

**Efficacy in partial-onset seizure subtypes**

Over the 12-week treatment period, the median percent reduction from baseline in partial-onset seizure frequency/week across all partial-onset seizure subtypes was numerically greater for BRV 20 mg/day and BRV 50 mg/day than for PBO, and was greatest among patients with secondarily generalized seizures (Fig. 2C). Similar results were obtained for the ≥50% responder rate (Fig. 2D).

**Effects of LEV use**

The median percent reduction from baseline in partial-onset seizure frequency/week and ≥50% responder rates for patients who were LEV-naive, had prior LEV use, and concomitant LEV use are provided in Table S1. For BRV, efficacy results across both variables were better than PBO only for patients who had previously used LEV (BRV 20 and 50 mg/day groups) and patients who were LEV-naive (all doses). The effect in patients using concomitant LEV was numerically smaller and suggestive of a limited effect of BRV when combined with LEV (Table S1).

**Safety and tolerability**

Overall, the incidence of treatment-emergent adverse events (TEAEs) was similar in all four treatment groups. At least one TEAE was reported during the treatment period by 69 (71.1%) of 97 patients on BRV 5 mg/day, 79 (79.0%) of 100 on BRV 20 mg/day, and 76 (75.2%) of 101 on BRV 50 mg/day. The majority of TEAEs were mild to moderate in intensity. Of the TEAEs reported by ≥5% patients, those reported in any BRV group with a frequency ≥3% higher than PBO were somnolence and dizziness (all three BRV doses); fatigue (BRV 20 and 50 mg/day); influenza (BRV 5 and 20 mg/day); nausea and urinary tract infection (BRV 20 mg/day); and diarrhea, insomnia, vomiting and nasopharyngitis (BRV 50 mg/day) (Table 3). No clear dose response was observed in the incidence of TEAEs across BRV dose groups.

During the 12-week treatment period, TEAEs led to permanent discontinuation of study medication in 20 patients: 2 (2.0%) in the PBO group compared with 8 (8.2%) in the BRV 5 mg/day group, 4 (4.0%) in the BRV 20 mg/day group, and 6 (5.9%) in the BRV 50 mg/day group. The most frequently reported type of TEAEs leading to permanent discontinuation were psychiatric disorders (0.0%, 5.2%, 1.0%, and 1.0% for PBO, BRV 5 mg/day, BRV 20 mg/day, and BRV 50 mg/day, respectively) and nervous system disorders (1%, 2.1%, 1%, and 3%, for PBO, BRV 5 mg/day, BRV 20 mg/day, and BRV 50 mg/day, respectively).

Psychiatric disorders reported by ≥1% of patients were insomnia (BRV 4.0% vs. PBO 2.0%), depression (BRV 3.7% vs. PBO 1.0%), irritability (BRV 3.7% vs. PBO 2.0%), anxiety (BRV 1.7% vs. PBO 1.0%), memory impairment (BRV 1.7% vs. PBO 1.0%), agitation (BRV 1.0% vs. PBO 0%), and depressed mood (BRV 1.0% vs. PBO 0%).

There was a possible dose-related trend in the incidence of drug-related TEAEs during the treatment period: 35.7% for PBO compared with 44.3% for BRV 5 mg/day, 46.0% for...
for BRV 20 mg/day, and 55.4% for BRV 50 mg/day. Severe AEs were reported by 26 patients during the treatment period: 5 (5.1%) in the PBO group, 8 (8.2%) in the BRV 5 mg/day group, 4 (4.0%) in the BRV 20 mg/day group, and 9 (8.9%) in the BRV 50 mg/day group. The incidence of treatment-emergent SAEs during the treatment period was higher in BRV-treated patients (2.3%) compared with PBO-treated patients (0.0%). A total of six patients reported seven nonfatal SAEs: one (1.0%) in the BRV 5 mg/day group (pneumonia), two (2.0%) in the BRV 20 mg/day group (bronchospasm and syncope), and three (3.0%) in the BRV 50 mg/day group (bronchitis, abdominal pain with pain and vomiting; chest pain with dyspnea; grand mal convulsion). Six of these SAEs were considered unrelated or unlikely to be related to the study medication.

Two deaths occurred during this study. One patient receiving BRV 20 mg/day died on the first day of the down titration period; following a seizure, the patient experienced cardiorespiratory arrest (cause of death certified as bronchoaspiration and acute respiratory failure). The second patient was randomized to receive BRV 50 mg/day but had permanently discontinued the study drug 2 weeks prior to death. After feeling unwell and going to bed, the patient was found face down and unresponsive, with no sign of seizures. After resuscitation, computed tomography revealed a large subarachnoid hemorrhage and 2 days later brain death was diagnosed. Autopsy revealed global hypoxic–ischemic encephalopathy.

Overall, there were no clinically significant changes from baseline for blood chemistry and urinalysis parameters,
physical and neurologic examinations, vital signs, body weight, and ECG measurements.

**DISCUSSION**

In this randomized, double-blind, placebo-controlled phase III study, the primary efficacy analysis showed a 12.8% reduction in baseline-adjusted partial-onset seizure frequency per week for BRV 50 mg/day over PBO \((p = 0.025)\). Results, however, were not significant for the lower doses of BRV 5 and 20 mg/day groups (−0.9% and 4.1%, respectively). These findings were mirrored in a post hoc analysis conducted to evaluate the partial-onset seizure frequency standardized to a 28-day period. Statistical significance was demonstrated for the BRV 50 mg/day group (22.0% reduction over PBO; \(p = 0.004\)), but not for BRV 5 and 20 mg/day (2.6% and 8.7%, respectively). Standardization of seizure frequency over longer (e.g., 28 days) rather than shorter (e.g., 7 days) periods has been used in several other phase III studies of AEDs in recent years (Ben-Menachem et al., 2007; Gil-Nagel et al., 2009; Halasz et al., 2009; Chung et al., 2010; French et al., 2012; Krauss et al., 2012). Standardizing seizure frequency to 28 days may better characterize treatment effect, as this can be underestimated when standardizing to a shorter duration. Furthermore, the longer time period may allow for normalization of any apparent PBO response.

Consistent with the primary efficacy analysis, the proportion of \(\geq 50\%\) responders was significantly higher for the 50 mg/day group compared with PBO, but not in the BRV 5 and 20 mg/day groups. Median percent reduction from baseline in partial-onset seizure frequency/week results were similar, and four patients (4.0%) in the BRV 50 mg/day group were seizure-free compared with none in the PBO group. Overall, these results demonstrate efficacy for the 50 mg/day BRV dose, and suggest a lesser effect at lower doses.

Results of an exploratory sub-analysis by seizure subtype indicated that in all three groups (simple partial, complex partial, and secondarily generalized) median percent reduction from baseline in seizure frequency/week and \(\geq 50\%\) responder rate were numerically higher for BRV 20 mg/day and BRV 50 mg/day compared with PBO. The difference between BRV and PBO was greatest for secondarily generalized seizures and smallest for complex partial seizures. However, the study was not powered to measure the efficacy of BRV in individual seizure subtypes; analysis of data from more patients is recommended before any further conclusions are drawn.

Across the efficacy variables, results of another sub-analysis by LEV use (LEV-naive, prior LEV, concomitant LEV) showed a greater numerical effect for BRV (20 and 50 mg/day) compared with PBO among patients who had previously received LEV or were LEV-naive at study entry. This observation had been noted in other studies of BRV (Biton et al., 2009; Kwan et al., 2009; French et al., 2010; van Paesschen et al., 2013), suggesting that concomitant LEV may reduce BRV efficacy. The overall incidence of TEAEs in this group did not raise any tolerability concerns (data not shown). However, patient numbers are not sufficient to allow firm conclusions to be drawn. The number of patients with concomitant LEV use at study entry was limited to 20% of the total study population per protocol; a small group of 56 patients received LEV in addition to BRV. A pooled analysis of data from all BRV phase IIb and III studies may be useful to assess this apparent effect in a more robust manner. From a study design perspective, the capacity of concomitant drugs’ mechanisms of action to influence outcomes may constitute a potential pitfall.
Two dose-ranging studies (N01114 and N01193) of adjunctive BRV have been completed previously, evaluating doses of 5, 20, 50, and 150 mg/day in patients with uncontrolled partial-onset seizures (French et al., 2010; van Paesschen et al., 2013). In the N01114 study, for BRV 50 and 150 mg/day, the primary efficacy outcome (percent reduction in baseline-adjusted partial-onset seizure frequency/week over PBO during the 7-week maintenance period) had no statistically significant differences between the placebo and the active groups; however, a clear differentiation from PBO was observed at the BRV 50 mg/day dose for several other efficacy outcomes (van Paesschen et al., 2013). In the N01193 study, a clear dose–response effect was observed for BRV, with the 50 mg/day dose demonstrating statistically significant efficacy versus PBO across a range of outcome measures (French et al., 2010). In contrast, the efficacy results shown previously in study N01193 (French et al., 2010), in the current study the 20 mg/day dose did not demonstrate significant improvements in median percent reduction from baseline in partial-onset seizure frequency/week and ≥50% responder rate compared with placebo. It is not unusual in clinical trials for certain doses to demonstrate efficacy in one study but not in another; examples are studies of lacosamide (Ben-Menachem et al., 2007), gabapentin (Sivenius et al., 1991), and carisbamate (Sperling et al., 2010). The variation of results across these studies might be attributed to multiple factors including patient and site selections, accuracy of diagnosis, sample size, and variations in study design.

BRV was generally well tolerated in this study. Only 18 patients of 396 used the fallback option: three patients in the PBO group, compared with four, five, and six patients in the BRV 5, 20, and 50 mg/day groups, respectively. The majority of patients (91.2%) completed the study and entered the open-label extension study (87.6%). The most commonly reported TEAEs in the BRV 50 mg/day group were somnolence, dizziness, headache, fatigue, and insomnia. No clear dose–response effect was observed with regard to tolerability, or among all patients who discontinued from the study. The most common type of TEAEs leading to premature discontinuation was psychiatric disorders, and no dose correlation was demonstrated. Nonpsychotic behavioral AEs, a subgroup of psychiatric disorders that has been previously reported for LEV (e.g., irritability and aggression), appeared to be reported to a lesser extent in the present study of BRV. However, there are no head-to-head studies that can confirm this observation, although a post hoc analysis of nonpsychotic behavioral TEAEs in LEV and BRV trials support this (D’Souza et al., 2012). In addition, there were no clinically significant changes from baseline in laboratory measures, vital signs, and ECG studies. The tolerability results of the current study are comparable to those of the two phase II studies (French et al., 2010; van Paesschen et al., 2013), demonstrating BRV to be well tolerated.

Similar to other studies, a potential limitation of this study is the refractory nature of epilepsy among the patients studied; 16.7% of patients had used five or more AEDs in the last 5 years. It should be noted that information about previous AED use was not collected beyond the last 5 years before study entry. The generalizability of the study results in other populations is also a consideration, as none of the patients enrolled were from Europe. However, there was geographic representation from five countries, including Australia, Canada, and the United States of America. Finally, as in all studies investigating partial-onset seizures, it may be difficult to establish the occurrence of a simple partial-onset seizure; however, this is not likely to have affected the overall trial outcome.

In conclusion, BRV 50 mg/day demonstrated statistically significant improvements compared with PBO across both primary and secondary efficacy endpoints. All BRV doses assessed appeared to be well tolerated without titration, and the completion rate was high.

Acknowledgments

This study was sponsored by UCB Pharma. UCB Pharma was involved in the design and conduct of the study, and collection, management, and analysis of the data. The authors thank the members of the N01253 Study Group and the patients who participated in the study for their contribution to the research; Laurent Turet, PhD (UCB Pharma), for critical review and coordination of the manuscript preparation; and David Sen, PhD (UCB Pharma), for providing statistical input. Sally Cotterill, PhD (QXV Communications, Macclesfield, United Kingdom) provided writing support, which was funded by UCB Pharma.

Disclosure

Victor Biton has been an investigator for Xenonport, Medivation, Dainippon, GSK, Genzyme, Astellas/Fujisawa, Myriad, RWJPRI, Insmed, Ortho McNeil, Jazz, Carter Wallace/MedPointe, Parke-Davis, HMR/Sanofi-Aventis, Novartis, IVAX, Abbott, AstraZeneca, Cyberonics, Schwabe, SkypePharma, NPS, Saegis, Eunoe, Genentech, Abbott, J&J, Marinus, Intranasal/Ikano, Ovation/Lundbeck, Schwarz/UCB, Valeant, XTL, Forest, Elan, Icaegen, Impax, Janssen, Medivation, Depomed, Vernalis, and Daiichi Sankyo. He has received consulting/lecture fees from Merck, Pfizer, Jazz, Upsher-Smith, Lundbeck, Eisai, Avigen, GSK, Ortho-McNeil, Icaegen, UCB/Schwarz, and Valeant. Sam Berkovic’s institution has received funding from UCB Pharma for clinical trials and support for travel to study meetings, and from a planned patent for PCDH19 testing. He has received honoraria from UCB Pharma to participate in educational symposia and advisory boards, and unrestricted educational grants for research retreats from UCB Pharma, Novartis, Sanofi-Aventis, and Jansen Cilag. He and his institution were also involved with a patent held by Bionomics Inc for SCN1A testing. Michael Sperling’s institution has received clinical trial funding from UCB Pharma; he has received consultancy fees by Upsher-Smith for trial design and payment as associate editor of Epilepsia. Bassel Abou-Khalil’s institution has received clinical trial funding from UCB Pharma. Martin Johnson and Sarah Lu are employees of UCB Pharma. We confirm that we have read the Journal’s position involved in ethical publication and affirm that this report is consistent with these guidelines.

References

Ben-Menachem E, Biton V, Jatuzis D, bou-Khalil B, Doty P, Rudd GD. (2007) Efficacy and safety of oral lacosamide as adjunctive therapy in adults with partial-onset seizures. Epilepsia 48:1308–1317.
Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. (2010) Progress report on new antiepileptic drugs: a summary of the Tenth Eilat Conference (EILAT X). Epilepsy Res 92:89–124.

Biton V, Werhahn KJ, Johnson ME, Falter U, Climos K, Schelstraete I, Brodsky A, von Rosenstiel P. (2009) Brivaracetam as adjunctive treatment of refractory partial-onset seizures in adults: results from two randomized, double-blind, placebo-controlled trials. Epilepsia 50 (Suppl. 11):106–107.

Brodsky A, Costantini C, von Rosenstiel P. (2007) Safety and tolerability of brivaracetam (ucb 34714) as adjunctive treatment in adults with refractory partial-onset seizures. Epilepsia 48(Suppl. 6):342.

Chung S, Sperling MR, Biton V, Krauss G, Hebert D, Rudd GD, Doty P. (2010) Lacosamide as adjunctive therapy for partial-onset seizures: a randomized controlled trial. Epilepsia 51:958–967.

D’Souza J, Johnson M, Borghs S. (2012) Meta-analysis of non-psychoactive behavioural treatment emergent adverse events in brivaracetam and levetiracetam development programmes. Epilepsia 53:118.

French JA, Costantini C, Brodsky A, von Rosenstiel P. (2010) Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. Neurology 75:519–525.

French JA, Krauss GL, Biton V, Squillacote D, Yang H, Laurenza A, Kumar D, Rogowski MA. (2012) Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology 79:589–596.

Gillard MR, Fuks B, Leclercq K, Matagne A. (2011) Binding characteristics of brivaracetam, a selective, high affinity SV2A ligand in rat, mouse and human brain: relationship to anti-convulsant properties. Eur J Pharmacol 664:36–44.

Gil-Nagel A, Lopes-Lima J, Almeida L, Maia J, Soares-da-Silva P. (2009) Efficacy and safety of 800 and 1200 mg eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures. Acta Neurol Scand 120:281–287.

Halasz P, Kalvaiainen R, Mazurkiewicz-Beldzinska M, Rosenow F, Doty P, Hebert D, Sullivan T. (2009) Adjunctive lacosamide for partial-onset seizures: efficacy and safety results from a randomized controlled trial. Epilepsia 50:443–453.

International League Against Epilepsy. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 30:389–399.

Kanda BM, Matagne AC, Talaga PE, Pasau PM, Differding E, Lallemand BI, Frycia AM, Moureau FG, Klitgaard HV, Gillard MR, Fuks B, Michel P. (2004) Discovery of 4-substituted pyrrolidone buanamides as new agents with significant antiepileptic activity. J Med Chem 47:530–549.

Krauss GL, Serratos JM, Villanueva V, Endziniene M, Hong Z, French J, Yang H, Squillacote D, Edwards HB, Zhu J, Laurenza A. (2012) Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology 78:1408–1415.

Kwan P, Van Wijck F, Milev U, Brodsky A, von Rosenstiel P. (2009) Safety and tolerability of brivaracetam as adjunctive treatment in adults with refractory epilepsy: randomized, double-blind, placebo-controlled trial. Epilepsia 50(Suppl. 11):107–108.

Matagne A, Margineanu D-G, Kenda B, Michel P, Klitgaard H. (2008) Anti-convulsive and anti-epileptic properties of brivaracetam (ucb 34714), a high-affinity ligand for the synaptic vesicle protein, SV2A. Br J Pharmacol 154:1662–1671.

Rolan P, Pigeolet E, Stockis A. (2004) UCB 34714: single and multiple rising dose safety, tolerability, and pharmacokinetics in healthy subjects. Epilepsia 45(Suppl. 7):314–315.

Rolan P, Sargentini-Maier ML, Pigeolet E, Stockis A. (2008) The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after multiple increasing oral doses in healthy males. Br J Clin Pharmacol 66:71–75.

Sargentini-Maier ML, Rolan P, Connell J, Tytgat D, Jacobs T, Pigeolet E, Riethuisen JM, Stockis A. (2007) The pharmacokinetics, CNS pharmacodynamics and adverse event profile of brivaracetam after single increasing oral doses in healthy males. Br J Clin Pharmacol 63:680–688.

Sivenius J, Kalvaiainen R, Ylenin A, Riekkinen P. (1991) Double-blind study of Gabapentin in the treatment of partial seizures. Epilepsia 32:539–542.

Sperling MR, Greenspan A, Cramer JA, Kwan P, Kalvaiainen R, Halford JJ, Schmitt J, Yuen E, Cook T, Haas M, Novak G. (2010) Carisbamate as adjunctive treatment of partial onset seizures in adults in two randomized, placebo-controlled trials. Epilepsia 51:333–343.

van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. (2013) Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase Ib, randomized, controlled trial. Epilepsia 54:89–97.

von Rosenstiel P, Perucca E. (2009) Brivaracetam. In Shorvon S, Perucca E, Engel J Jr (Eds.) The treatment of epilepsy. Wiley-Blackwell, Chichester, pp. 447–457.

**Supporting Information**

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

**Table S1.** Median percent reduction from baseline in seizure frequency/week and ≥50% responder rate stratified by levetiracetam use.

**Figure S1.** Study design.