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Efficacy, safety, and tolerability of adjunctive brivaracetam for secondarily generalized tonic-clonic seizures: Pooled results from three Phase III studies

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ABSTRACT

Purpose: Secondarily generalized tonic-clonic seizures (SGTCS) are among the most devastating types of seizures, contributing to increased morbidity and mortality. Brivaracetam (BRV), a selective, high-affinity ligand for synaptic vesicle 2A (SV2A), has been shown to be useful for the adjunctive treatment of focal seizures. We sought to determine its specific efficacy in treating SGTCS.

Methods: Data were pooled from three Phase III studies (NCT00490035; NCT00464269; NCT01261325) of adults with focal seizures taking 1–2 antiepileptic drugs (AEDs) who received placebo or BRV 50–200 mg/day without titration over a 12-week treatment period. We report efficacy and safety/tolerability data for the BRV therapeutic dose range (50–200 mg/day) in patients with focal seizures including baseline SGTCS.

Results: Patients (efficacy population, $N = 409$) had been diagnosed with epilepsy for a mean ± standard deviation duration of 22.2 ± 13.1 years. Baseline median SGTCS frequency was 3.0 per 28 days. The majority (293, 71.6%) had failed ≥2 AEDs prior to study enrollment. The median percent reduction from baseline in SGTCS frequency/28 days was: placebo, 33.3%; BRV 50 mg/day, 66.6% ($p < 0.001$); BRV 100 mg/day, 61.2% ($p = 0.002$); and BRV 200 mg/day, 82.1% ($p < 0.001$). The ≥50% responder rate for SGTCS was: placebo, 33.0%; BRV 50 mg/day, 61.3% ($p = 0.003$); BRV 100 mg/day, 55.0% ($p < 0.001$); and BRV 200 mg/day, 64.0% ($p < 0.001$). Freedom from SGTCS was achieved by: placebo, 14.8%; BRV 50 mg/day, 22.6%; BRV 100 mg/day, 31.0%; and BRV 200 mg/day, 36.0% of patients. Time to first SGTCS during the treatment period was longer in patients receiving BRV than placebo (26 days vs 8 days, hazard ratio 0.55, $p < 0.001$). In the SGTCS safety population ($N = 487$), treatment-emergent adverse events (TEAEs) were reported by 60.6% of patients receiving placebo vs 65.0% of patients receiving BRV ≥50 mg/day. Serious TEAEs were reported by 3.1% placebo vs 3.9% BRV ≥50 mg/day. Discontinuations due to TEAEs were 3.9% placebo vs 6.3% BRV ≥50 mg/day.

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Conclusions: In patients with drug-resistant focal seizures, adjunctive BRV is effective in reducing the frequency of SGTCS. Almost one-third (30.4%) of patients were rendered completely free of SGTCS during the 12-week treatment period when taking BRV ≥50 mg/day. BRV was well tolerated, with a TEAE profile consistent with that of the overall study population.

1. Introduction

Patients with drug-resistant focal epilepsy are at increased risk for a number of physical and psychosocial complications. Such risks are heightened when their uncontrolled seizures secondarily generalize. Given the increased risk of falls associated with generalized tonic-clonic seizures (GTCS), such seizures carry a 2.9 relative risk for injuries, in a univariate regression analysis adjusted for seizure frequency (Lawn et al., 2004). GTCS also increase the risk of associated head trauma (Beghi, 2009; Nakken and Lossius, 1993; Neufeld et al., 1999) and fractures (Persson et al., 2002). In addition, lower quality of life (QOL) has been observed in patients with GTCS. This is captured by poorer scores relating to work/social function, energy/fatigue, health discouragement, emotional well-being, seizure worry, social isolation, health perception, bodily pains, social support, overall health, and overall QOL (Shetty et al., 2011; Viteva, 2014). After adjusting for individual psychological comorbidities, seizure severity has been shown to be the strongest predictor of psychosocial variables including anxiety, self-esteem, and locus of control (Smith et al., 1991). Most importantly, GTCS are known to increase the risk of mortality, with a hazard ratio approaching 6.2 in a patient population newly diagnosed with epilepsy (Lhatoo et al., 2001). Intractable convulsive seizures are regarded as one of the strongest risk factors for sudden unexpected death in epilepsy (SUDEP) (Devinsky, 2011; Hirsch et al., 2011; Laxer et al., 2014; Shorvon and Tomson, 2011). This has resulted in such seizures being included in historical risk factor inventories for this dreaded phenomenon (DeGiorgio et al., 2010).

When patients with drug-resistant focal seizures are not candidates for resective epilepsy surgery, physicians often rely on newer antiepileptic drugs (AEDs) to try and improve seizure control. One of the latest AEDs to be approved for adjunctive treatment of focal seizures is brivaracetam (BRV). BRV is a synaptic vesicle 2A (SV2A) ligand, with a 10- to 30-fold increased affinity for SV2A compared to levetiracetam (Gillard et al., 2011; Kenda et al., 2004; Malykh and Sadaie, 2010). In three Phase III clinical trials, adjunctive therapy with BRV at doses ranging from 50 to 200 mg/day significantly reduced the frequency of focal seizures (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). Given its mechanism of action, no requirement to titrate, and overall tolerability, BRV is a potentially useful treatment for patients with drug-resistant focal seizures. However, the specific efficacy of BRV in reducing secondarily generalized tonic-clonic seizures (SGTCS) has not been robustly explored. Although the results of the individual Phase III trials suggested efficacy for SGTCS, they were not powered to detect significant differences in reductions of specific seizure subtypes. A pooled analysis is needed to more definitively determine the effectiveness of BRV at different therapeutic doses in reducing the frequency of these debilitating seizures.

Given the increased morbidity and mortality associated with SGTCS, we performed a post-hoc analysis of pooled Phase III clinical trial data on the effects of BRV on this specific seizure subtype. We sought to determine the efficacy, safety, and tolerability of BRV in patients with focal seizures including baseline SGTCS.

2. Materials and methods

2.1. Study design

This was a post-hoc analysis of patients with SGTCS among their baseline seizures from pooled data of three Phase III trials; data for the approved BRV dosages (50–200 mg/day) are reported. All trials were prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group, fixed-dose studies (NCT00490035, NCT00464269, and NCT01261325). Each study consisted of an 8-week prospective baseline period and 12-week treatment period. These were followed by a variable (1- to 4-week) down-titration and subsequent drug-free period, or entry into an optional open-label, long-term follow-up study (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). At the conclusion of the baseline period, patients were randomized to receive placebo (PBO) or BRV (5, 20, 50, 100, or 200 mg/day, dependent on the study) administered in two equally divided doses without titration. All studies were conducted in accordance with the International Conference on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki. All study protocols were approved by institutional review boards at participating study sites. Written informed consent was obtained from all patients prior to enrollment. For complete details of individual study design, please refer to studies NCT00490035, NCT00464269, and NCT01261325 (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014).

2.2. Study population

Patients aged ≥16–70 years (Biton et al., 2014; Ryvlin et al., 2014) or aged ≥16–80 years (Klein et al., 2015) were eligible for study enrollment provided they had well- characterized focal seizures or a focal epilepsy syndrome. Their focal seizures had to be uncontrolled despite 1–2 concomitant AEDs at stable and optimal doses for ≥1 month prior to the first study visit. At least 2 focal seizures/month for the 3 months prior to screening and ≥8 focal seizures during the 8-week prospective baseline period were required for eligibility. In addition, patients were required to have ≥2 focal seizures in each 4-week interval of the baseline period in study NCT01261325. For complete inclusion and exclusion criteria, please refer to studies NCT00490035, NCT00464269, and NCT01261325 (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). Patients with SGTCS among their baseline seizures, whether or not they had other types of seizure, were included in this post-hoc analysis.

2.3. Efficacy assessments

Seizure occurrence was assessed via patient reporting on daily record cards. These cards were reviewed by investigators at each study visit. Outcomes for the current post-hoc analysis included median percent reduction in SGTCS/28 days, ≥50% and ≥75% responder rates for SGTCS, freedom from SGTCS, and time to first SGTCS as assessed during the 12-week treatment period. The ≥50% responder rates for focal seizures without impairment of aware-

Table 1
Demographics and baseline characteristics of patients with baseline secondary generalized tonic-clonic seizures (efficacy population).

	Placebo (n = 115)	BRV 50 mg/day (n = 62)	BRV 100 mg/day (n = 100)	BRV 200 mg/day (n = 75)	BRV ≥50 mg/day (n = 237)
Age (years), mean (SD)	35.8 (12.8)	35.3 (12.7)	37.8 (12.3)	38.1 (12.9)	37.2 (12.6)
Female, n (%)	54 (47.0)	29 (46.8)	49 (49.0)	36 (48.0)	114 (48.1)
Race, white, n (%)	78 (67.8)	46 (74.2)	65 (65.0)	58 (77.3)	169 (71.3)
BMI (kg/m^2), mean (SD)	25.8 (6.1)	24.6 (4.7)	26.9 (6.3)	26.2 (6.6)	26.1 (6.1)
Baseline seizure frequency Focal					
Mean (SD)/28 days	16.3 (18.7)	16.7 (22.7)	15.5 (19.4)	22.8 (62.4)	18.1 (39.0)
Median/28 days	9.4	9.3	8.5	7.5	8.3
SGTC					
Mean (SD)/28 days	5.1 (6.1)	5.5 (6.1)	5.2 (6.6)	2.9 (3.2)	4.5 (5.7)
Median/28 days	3.2	3.5	3.0	1.6	2.8
Prior AEDs, n (%)					
0–1	36 (31.3)	22 (35.5)	25 (25.0)	12 (16.0)	59 (24.9)
2–4	42 (36.5)	30 (48.4)	32 (32.0)	30 (40.0)	92 (38.8)
≥5	37 (32.2)	10 (16.1)	43 (43.0)	33 (44.0)	86 (36.3)
Concomitant AEDs, n (%)					
1	26 (22.6)	10 (16.1)	19 (19.0)	19 (25.3)	48 (20.3)
2	83 (72.2)	44 (71.0)	72 (72.0)	54 (72.0)	170 (71.7)
>2	6 (5.2)	8 (12.9)	9 (9.0)	2 (2.7)	19 (8.0)

AED = antiepileptic drug; BMI = body mass index; BRV = brivaracetam; SD = standard deviation; SGTC = secondary generalized tonic-clonic.

ness (Type IA) and focal dyscognitive seizures (Type IB) were also assessed in patients with baseline SGTCS.

2.4. Safety and tolerability assessments

Treatment-emergent adverse events (TEAEs) were recorded at each study visit. In addition to being questioned about TEAEs at each study visit, patients could spontaneously report TEAEs at any point during the treatment period. TEAEs were classified as mild, moderate, or severe and whether or not they were attributable to study medication. TEAEs were deemed serious when they resulted in death, were life-threatening, required hospitalization, resulted in persistent or significant disability/incapacity, or resulted in congenital anomalies/birth defects.

2.5. Statistical methods

A post-hoc analysis was performed on patients with ≥1 SGTCS recorded during the 8-week prospective baseline period who had received the BRV dosages 50–200 mg/day.

Percent reduction from baseline in SGTCS frequency/28 days was assessed by Hodges–Lehmann non-parametric effect estimates between BRV treatment groups and placebo. Responder rates were evaluated by logistic regression with 28-day adjusted seizure frequency for the treatment period as the outcomes, effects for treatment and study, and log-transformed baseline seizure frequency as a continuous covariate. Freedom from SGTCS was defined as no SGTCS being reported over the entire 12-week treatment period for patients who had completed their seizure diaries on all days. Time to first SGTCS was determined using patient seizure diary information from the start to the last day study drug was administered during the treatment period. Patients who discontinued during the treatment period were censored; the censored date was based on date of study drug discontinuation. Hazard ratios and treatment group comparisons were obtained from a semi-parametric hazards regression model with number of days to the first SGTCS as the outcome and an effect for treatment, and log-transformed baseline SGTCS frequency as a continuous covariate. Kaplan-Meier survival curves and estimates were generated for the 12-week treatment period. P-values were nominal because of the exploratory nature of the analysis; the alpha level was set at 0.05.

Given that BRV doses of 50–200 mg/day are considered therapeutic, all efficacy and TEAE analyses were performed for PBO versus BRV 50–200 mg/day. For all variables examined, results are separately reported as PBO versus BRV 50, 100, and 200 mg/day.

The safety population comprised all patients who had taken ≥1 dose of study drug and had baseline SGTCS. The efficacy population comprised all patients from the primary efficacy analyses who had baseline SGTCS. Patients receiving concomitant levetiracetam (LEV) were excluded (Biton et al., 2014; Ryvlin et al., 2014) for consistency with the trial which did not include patients taking concomitant LEV (Klein et al., 2015).

3. Results

3.1. Patient demographics and baseline characteristics

A total of 409 subjects with baseline histories of SGTCS comprised the efficacy population [222 men (54.3%) and 187 women (45.7%)]. The average age ± standard deviation (SD) at study enrollment was 36.4 ± 12.6 years. The mean ± SD duration of epilepsy of all participants in the efficacy population was 22.2 ± 13.1 years. The majority (293, 71.6%) of participants had failed ≥2 AEDs prior to randomization. The baseline median SGTCS frequency/28 days was 3.0 seizures. For a complete listing of all patient demographics of subjects with baseline histories of SGTCS receiving PBO and therapeutic doses of BRV, see Table 1.

3.2. Efficacy for SGTCS

Median percent reduction from baseline in SGTCS frequency/28 days during the treatment period varied by daily BRV dosage. This included a median percent reduction in SGTCS of 66.6% for 50 mg/day (n = 62, p < 0.001), 61.2% for 100 mg/day (n = 100, p = 0.002), and 82.1% for 200 mg/day (n = 75, p < 0.001) versus 33.3% for PBO (n = 115, see Table 2). This indicates that median SGTCS frequencies were reduced from baseline to 2.1 (PBO) versus 1.2, 1.2, and 0.3 SGTCS/28 days for BRV 50, 100, and 200 mg/day, respectively.

Doses of BRV ≥50 mg/day were associated with a significantly greater ≥50% responder rate than PBO (141/237, 59.5% vs 38/115, 33.0%, p < 0.0001). This difference remained significant for individual BRV doses of 50 mg/day (38/62, 61.3%, p = 0.003), 100 mg/day (55/100, 55.0%, p < 0.001), and 200 mg/day (48/75, 64%, p < 0.001, see Fig. 1). Therapeutic doses of BRV were also associated with a significantly greater ≥75% responder rate than PBO (106/237, 44.7%

Table 2
Median percent reduction from baseline in secondary generalized tonic-clonic seizures/28 days during the 12-week treatment period (efficacy population).

	Placebo (n = 115)	BRV 50 mg/day (n = 62)	BRV 100 mg/day (n = 100)	BRV 200 mg/day (n = 75)	BRV ≥50 mg/day (n = 237)
Median percent reduction from baseline in SGTCS/28 days	33.3	66.6	61.2	82.1	67.5
Median difference vs placebo		28.4	25.1	38.9	29.4
95% CI (LL, UL)		(11.0, 45.0)	(6.0, 43.6)	(16.1, 53.1)	(14.6, 43.8)
P-value		<0.001	0.002	<0.001	<0.001

BRV = brivaracetam; CI = confidence interval; LL = lower limit; SGTCS = secondary generalized tonic-clonic seizure; UL = upper limit.

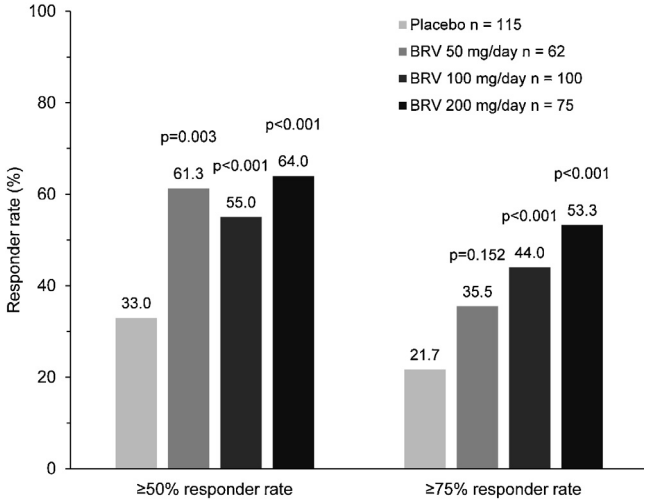

Fig. 1. ≥50% and ≥75% responder rates for secondary generalized tonic-clonic seizures during the 12-week treatment period (efficacy population). *P*-values are versus placebo.

vs 25/115, 21.7%, $p < 0.001$). Although the ≥75% responder rate for BRV 50 mg/day did not reach statistical significance (22/62, 35.5%, $p = 0.152$), it was significant for daily doses of 100 mg (44/100, 44.0%, $p < 0.001$) and 200 mg (40/75, 53.3%, $p < 0.001$, see Fig. 1).

Complete freedom from SGTCS in those with SGTCS during the baseline period was achieved by 17/115 patients (14.8%) receiving PBO versus 72/237 patients (30.4%; $p = 0.001$) receiving therapeutic doses of BRV during the 12-week treatment period. Complete SGTCS freedom rates increased in a dose-dependent fashion as the dose of BRV increased from 50 mg/day (14/62, 22.6%) to 100 mg/day (31/100, 31.0%) to 200 mg/day (27/75, 36.0%, see Fig. 2). Furthermore, low incidences of new-onset SGTCS during the treatment period were seen in patients treated with placebo (8/303) and BRV 50 mg/day, 100 mg/day and 200/mg day (8/99, 6/232 and 0/174, respectively) who were free from SGTCS during the 8-week baseline period (Klein et al., 2015).

Receiving therapeutic doses of BRV resulted in a significantly longer time to first SGTCS during the treatment period than PBO (26 vs 8 days, hazard ratio 0.55, 95% confidence interval 0.42, 0.71, $p < 0.001$). This remained significant when the individual therapeutic doses ranging from 50 to 200 mg/day were examined (Table 3). Based on Kaplan-Meier estimates of the percentage of patients completing specified durations of treatment (Fig. 3), 32.9% of patients receiving therapeutic doses of BRV remained free of SGTCS for 12 weeks versus 15.0% of those receiving PBO (see Supplemental Table S1).

In patients with baseline SGTCS, reductions in other types of focal seizures without secondary generalization (with or without impairment of consciousness) was generally greater than PBO. Information regarding ≥50% responder rates for focal seizures without impairment of awareness and focal dyscognitive seizures in those with baseline SGTCS is presented in Supplemental Tables S2 and S3.

3.3. Safety and tolerability

A total of 487 subjects with baseline histories of SGTCS comprised the safety population. The numbers of patients reporting TEAEs were similar between those patients receiving PBO (77/127, 60.6%) and those receiving BRV ≥50 mg/day (165/254, 65.0%). Drug-related TEAEs were recorded in 100/254 patients (39.4%) receiving BRV ≥50 mg/day (vs 41/127, 32.3% receiving PBO). Serious TEAEs were reported by 10/254 patients (3.9%) receiving therapeutic doses of BRV, and were considered by the investigator to be drug-related in 3 (1.2%) patients. This is similar to the 4/127 patients (3.1%) receiving PBO who reported serious TEAEs, and were considered to be drug-related in 1 (0.8%) patient. Study medication discontinuation secondary to TEAEs occurred in 16/254 patients (6.3%) receiving BRV ≥50 mg/day versus 5/127 patients (3.9%) receiving PBO. The most commonly reported side effects in those receiving therapeutic doses of BRV included somnolence (12.6%), headache (11.0%), dizziness (8.3%), fatigue (7.9%), and nausea (5.9%). Such safety and tolerability data in the SGTCS safety population were consistent with corresponding data from the pooled Phase III studies examining all focal seizure subtypes (Ben-Menachem et al., 2016).

During the three Phase III trials, four patients with baseline history of SGTCS died. One patient was in the PBO group, two were randomized to BRV 200 mg/day and one was randomized to BRV 50 mg/day. All deaths in the BRV-treated patients were classified as SUDEP and occurred 1–14 days following the last confirmed dose of BRV.

4. Discussion

The results of this analysis indicate that adjunctive treatment with BRV appears to be effective in reducing the frequency of SGTCS with an indication of dose-dependence. Patients treated with doses of BRV ranging from 50 to 200 mg/day without titration were significantly more likely to achieve a ≥50% reduction in the frequency of this severe seizure subtype compared with those treated with PBO. The efficacy of BRV in reducing the frequency of SGTCS was demonstrated at multiple endpoints, and nearly one-third of patients achieved freedom from SGTCS during the 12-week treatment period. Such efficacy in reducing SGTCS was not associated with higher rates of TEAEs than those reported in the overall study population with focal seizures.

The ability of SGTCS reduction to improve the overall health and QOL of patients with drug-resistant focal epilepsy cannot be overstated. Even when complete seizure freedom is not achievable, a meaningful reduction in SGTCS has the potential to improve the life expectancy, health, and QOL of patients (Moschetta and Valente, 2013; Sperling et al., 2016). GTCS are associated with worsened memory function (Witt and Helmstaedter, 2012), and frequency of GTCS is linked to cognitive decline (Thompson and Duncan, 2005). Conversely, periods of remission have been associated with better

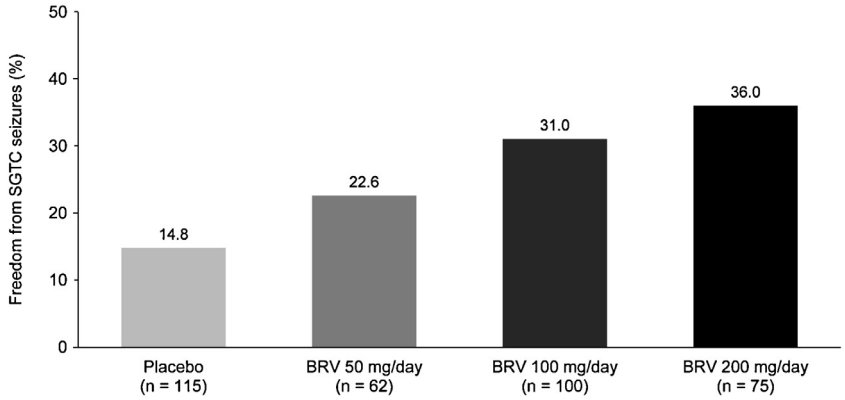

Fig. 2. Complete freedom from secondary generalized tonic-clonic seizures during the 12-week treatment period (efficacy population).

Table 3
Time to onset of first secondary generalized tonic-clonic seizures during the 12-week treatment period (efficacy population).

	Placebo (n = 115)	BRV 50 mg/day (n = 62)	BRV 100 mg/day (n = 100)	BRV 200 mg/day (n = 75)	BRV ≥50 mg/day (n = 237)
Time to first seizure, median (days)	8	23	17	56	26
95% CI (LL, UL)		(0.39, 0.79)	(0.43, 0.80)	(0.34, 0.71)	(0.42, 0.71)
P-value		0.001	<0.001	<0.001	<0.001

BRV = brivaracetam; CI = confidence interval; LL = lower limit; UL = upper limit.

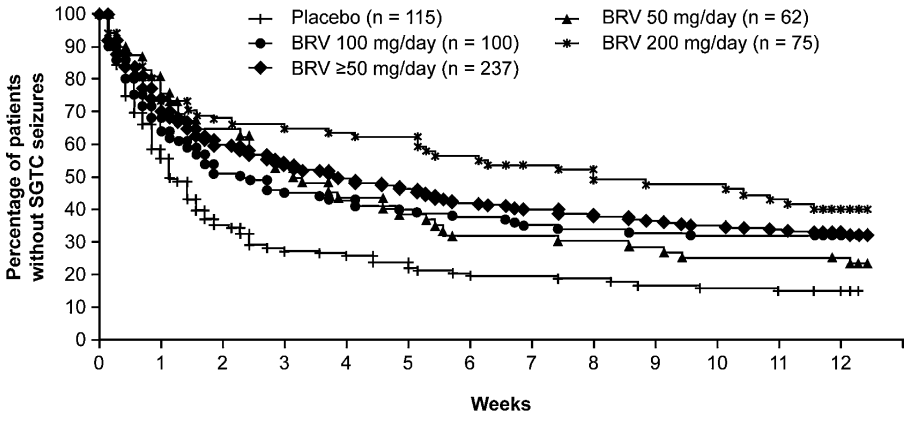

Fig. 3. Kaplan-Meier survival plots of time to onset of first secondarily generalized tonic-clonic seizure during the 12-week treatment period (efficacy population).

cognitive outcomes (Thompson and Duncan, 2005). Equally important, a reduction in SGTCS may help to reduce seizure-related injury and death. Continued GTCS are associated with a >10-fold increase in the rate of minor injuries, with an almost 3-fold increase in the rate of severe injuries versus healthy controls (Asadi-Pooya et al., 2012). In a study of resective epilepsy surgery outcomes, it was observed that significant palliation of SGTCS was a worthwhile goal, even when complete seizure freedom was not achievable. Reducing the occurrence of SGTCS to ≤2 per year was associated with a significant reduction in mortality, comparable to that of seizure-free patients (Sperling et al., 2016). Population-based studies have shown that decreasing GTCS frequency from >3/year to 1–3/year may be associated with a greater than 3-fold decrease in the odds of dying from SUDEP (Sperling et al., 2016; Walczak et al., 2001). When resective epilepsy surgery is not possible or unsuccessful, physicians will endeavor to explore newer pharmacologic options to gain the best control of drug-resistant SGTCS possible. Treatment with BRV 50–200 mg/day for 12 weeks resulted in significant reduction in the mean number of GTCS versus PBO in the current analysis, although the final numbers exceed the goal of 2 or 3 GTCS or fewer per year, which appears to be associated with reduced mortality (Sperling et al., 2016; Walczak et al., 2001). However, since GTCS are linked to falls, head injuries, and other trauma, any reduction is likely to lead to reduced morbidity if not mortality.

In various experimental animal models of epilepsy, BRV has been demonstrated to have higher potency and efficacy than LEV as both an anti-seizure and anti-epileptogenic agent (Matagne et al., 2008). However, the anti-epileptogenic effects have not yet been studied in other clinically relevant animal models or human subjects and hence, data are yet to be translated to show clinical significance. A direct comparison of BRV and LEV on SGTCS control in humans has not been performed. However, review of Phase III data yields interesting results. In a post-hoc analysis of pooled data from three Phase III trials, daily doses of LEV ranging from 1000 to 3000 mg were found to result in a 68.5% median reduction from baseline in SGTCS (Leppik et al., 2003). The efficacy of BRV and LEV in significantly reducing SGTCS suggests that SV2A may be an effective target when attempting to reduce seizure propagation/generalization. This may be secondary to the widespread expression of SV2A in the brain. This includes sites such as the dentate gyrus, entorhinal cortex, frontal cortex, several thalamic nuclei, and mesencephalon (Douaud et al., 2011; Fuks et al., 2003; Hanaya et al., 2012), which are often essential for seizure generation or propagation (Milton and Jung, 2003). Previous models of both

focal and generalized seizures have suggested that the SV2A protein is essential for neuronal synchronization (Kaminski et al., 2008). Given that BRV has a 10- to 30-fold increased affinity for SV2A vs LEV (Kenda et al., 2004; Malykh and Sadaie, 2010), this new AED may represent a superior way to exploit this specific antiepileptic mechanism of action.

As with some other newer AEDs, BRV appears to be a useful therapeutic option to reduce the frequency of SGTCS. At approved doses of 200 and 400 mg/day, lacosamide has been demonstrated to reduce SGTCS per 28 days from baseline by a median of 50.0–55.6% vs 32.5% for placebo. Higher reductions in SGTCS of 85.9% were only reported when lacosamide doses of 600 mg/day (which exceed the maximum FDA approved daily dose) but were administered under the supervision of the investigators in the course of these pivotal clinical trials (Sperling et al., 2014). Based on data pooled from three pivotal trials, the ≥50% responder rate for lacosamide has been reported as 50.9% (200 mg/day), 53.5% (400 mg/day), and 64.7% (600 mg/day) vs 36.6% (PBO) (Sperling et al., 2014). In a pooled analysis of three Phase III trials examining its efficacy for focal seizures, perampanel was associated with median percent reductions in SGTCS of 48.6% (4 mg/day), 62.9% (8 mg/day), and 53.3% (12 mg/day) vs 19.4% for PBO (Ko and Ramsay, 2013). The ≥50% responder rate for SGTCS was 49.3%, 60.5%, and 53.7% for perampanel 4 mg/day, 8 mg/day, and 12 mg/day, respectively, and 37.0% for PBO (Ko and Ramsay, 2013). In a secondary analysis of one pivotal Phase III study, eslicarbazepine acetate (ESL) resulted in an overall reduction in the median number of SGTCS during the 12-week maintenance period. This included a reduction from 1.5 to 1.2 in the ESL 1200 mg/day group, from 2.5 to 0.9 in the ESL 800 mg/day group, and from 3.2 to 2.7 in the ESL 400 mg/day group (vs 2.5–1.8 in the PBO group) (Elger et al., 2009). Such comparisons illustrate that SV2A binding appears to have comparable efficacy to other mechanisms of action, including sodium channel inactivation and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonism, in reducing the secondary generalization of focal seizures. Unfortunately, data regarding the efficacy of other AEDs such as clonazepam and ezogabine for SGTCS in similarly designed phase III trials is not readily available.

Our study is not without limitations. These data represent a post-hoc analysis of pooled data from three Phase III trials examining the efficacy of BRV on all focal onset seizure subtypes. The individual studies were powered to detect significant differences in focal onset seizures aggregately, not specific seizure subtypes. With a larger overall sample size of patients with baseline SGTCS, it is possible that trends in overall median percentage reductions in SGTCS in those receiving therapeutic doses of BRV would have reached statistical significance. A larger sample size would have also potentially permitted statistical analysis of data from patients who achieved complete freedom from SGTCS. Furthermore, long term efficacy and safety data in this population were not examined in this post-hoc analysis. Despite the smaller sample size, the post-hoc analysis was still able to demonstrate significantly larger percentages of patients achieving ≥50% reductions in SGTCS. Given the potential for such meaningful reductions to improve the overall health and QOL of those living with refractory SGTCS, these findings deserve notice.

5. Conclusions

BRV appears to be effective in reducing the frequency of SGTCS in a dose-dependent manner. Such results support the adjunctive use of BRV to treat uncontrolled SGTCS. These results hint at the effectiveness of targeting the SV2A as a means of reducing the generation and propagation of focal seizures. Given the increased morbidity and mortality associated with this seizure subtype, the importance of such reductions cannot be overemphasized.

Disclosures

Dr Moseley has received previous research support from the Mayo Clinic Department of Neurology Research Fund. He has performed previous consulting work for Nonin Medical, Inc. He has served on an advisory board for UCB Pharma and Validus Pharmaceuticals. He serves on speakers' bureaus for Cyberonics (LivaNova), Eisai, and UCB Pharma. Dr Asadi-Pooya has performed consulting work for UCB Pharma. Dr Sperling's institution has received research contracts from Acorda Therapeutics, Brain Sentinel, Eisai, GlaxoSmithKline, Lundbeck, Marinus Pharmaceuticals Inc, Medtronic, Neurelis, Pfizer, SK Life Science, Sunovion Pharmaceuticals Inc, UCB Pharma, and Upsher-Smith Laboratories Inc. Dr Diaz and Mr Elmoufti are employees of UCB Pharma. Dr Schiemann was an employee of UCB Pharma at the time the original studies and this analysis were conducted; he is currently an employee of Teva Pharmaceuticals. Dr Whitesides is an employee of UCB Pharma and reports personal fees from UCB Pharma outside the submitted work.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eplepsyres.2016.09.003.

References

Asadi-Pooya, A.A., Nikseresht, A., Yaghoubi, E., Nei, M., 2012. Physical injuries in patients with epilepsy and their associated risk factors. Seizure 21, 165–168.
Beghi, E., 2009. Accidents and injuries in patients with epilepsy. Expert Rev. Neurother. 9, 291–298.
Ben-Menachem, E., Mameniskiene, R., Quarato, P.P., Klein, P., Gamage, J., Schiemann, J., Johnson, M.E., Whitesides, J., McDonough, B., Eckhardt, K., 2016. Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical studies. Neurology 87, 314–323.
Biton, V., Berkovic, S.F., Abou-Khalil, B., Sperling, M.R., Johnson, M.E., Lu, S., 2014. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia 55, 57–66.
DeGiorgio, C.M., Miller, P., Meymandi, S., Chin, A., Epps, J., Gordon, S., Gornbein, J., Harper, R.M., 2010. RMSSD, a measure of vagus-mediated heart rate variability, is associated with risk factors for SUDEP: the SUDEP-7 Inventory. Epilepsy Behav. 19, 78–81.
Devinsky, O., 2011. Sudden, unexpected death in epilepsy. N. Engl. J. Med. 365, 1801–1811.
Douaud, M., Feve, K., Pituello, F., Gourichon, D., Boitard, S., Leguern, E., Coquerelle, G., Vieaud, A., Batini, C., Naquet, R., Vignal, A., Tixier-Boichard, M., Pitel, F., 2011. Epilepsy caused by an abnormal alternative splicing with dosage effect of the SV2A gene in a chicken model. PLoS One 6, e26932.
Elger, C., Halasz, P., Maia, J., Almeida, L., Soares-da-Silva, P., 2009. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with

refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. Epilepsia 50, 454–463.
Fuks, B., Gillard, M., Michel, P., Lynch, B., Vertongen, P., Leprince, P., Klitgaard, H., Chatelain, P., 2003. Localization and photoaffinity labelling of the levetiracetam binding site in rat brain and certain cell lines. Eur. J. Pharmacol. 478, 11–19.
Gillard, M., 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.
Hanaya, R., Hosoyama, H., Sugata, S., Tokudome, M., Hirano, H., Tokimura, H., Kurisu, K., Serikawa, T., Sasa, M., Arita, K., 2012. Low distribution of synaptic vesicle protein 2A and synaptotagimin-1 in the cerebral cortex and hippocampus of spontaneously epileptic rats exhibiting both tonic convulsion and absence seizure. Neuroscience 221, 12–20.
Hirsch, L.J., Donner, E.J., So, E.L., Jacobs, M., Nashef, L., Noebels, J.L., Buchhalter, J.R., 2011. Abbreviated report of the NIH/NINDS workshop on sudden unexpected death in epilepsy. Neurology 76, 1932–1938.
Kaminski, R.M., Matagne, A., Leclercq, K., Gillard, M., Michel, P., Kenda, B., Talaga, P., Klitgaard, H., 2008. SV2A protein is a broad-spectrum anticonvulsant target: functional correlation between protein binding and seizure protection in models of both partial and generalized epilepsy. Neuropharmacology 54, 715–720.
Kenda, B.M., Matagne, A.C., Talaga, P.E., Pasau, P.M., Differding, E., Lallemand, B.I., Frycia, A.M., Moureau, F.G., Klitgaard, H.V., Gillard, M.R., Fuks, B., Michel, P., 2004. Discovery of 4-substituted pyrrolidone butanamides as new agents with significant antiepileptic activity. J. Med. Chem. 47, 530–549.
Klein, P., Schiemann, J., Sperling, M.R., Whitesides, J., Liang, W., Stalvey, T., Brandt, C., Kwan, P., 2015. 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. Epilepsia 56, 1890–1898.
Ko, D., Ramsay, R.E., 2013. Perampanel: expanding therapeutic options for patients with medically refractory secondary generalized convulsive seizures. Acta Neurol. Scand. Suppl., 36–43.
Lawn, N.D., Bamlet, W.R., Radhakrishnan, K., O'Brien, P.C., So, E.L., 2004. Injuries due to seizures in persons with epilepsy: a population-based study. Neurology 63, 1565–1570.
Laxer, K.D., Trinka, E., Hirsch, L.J., Cendes, F., Langfitt, J., Delanty, N., Resnick, T., Benbadis, S.R., 2014. The consequences of refractory epilepsy and its treatment. Epilepsy Behav. 37, 59–70.
Leppik, I.E., Biton, V., Sander, J.W., Wieser, H.G., 2003. Levetiracetam and partial seizure subtypes: pooled data from three randomized, placebo-controlled trials. Epilepsia 44, 1585–1587.
Lhatoo, S.D., Johnson, A.L., Goodridge, D.M., MacDonald, B.K., Sander, J.W., Shorvon, S.D., 2001. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. Ann. Neurol. 49, 336–344.
Malykh, A.G., Sadaie, M.R., 2010. Piracetam and piracetam-like drugs: from basic science to novel clinical applications to CNS disorders. Drugs 70, 287–312.
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.
Milton, J., Jung, P., 2003. Epilepsy as a Dynamic Disease, 1 ed. Springer-Verlag, Berlin, Heidelberg.
Moschetta, S., Valente, K.D., 2013. Impulsivity and seizure frequency, but not cognitive deficits, impact social adjustment in patients with juvenile myoclonic epilepsy. Epilepsia 54, 866–870.
Nakken, K.O., Lossius, R., 1993. Seizure-related injuries in multihandicapped patients with therapy-resistant epilepsy. Epilepsia 34, 836–840.
Neufeld, M.Y., Vishne, T., Chistik, V., Korczyn, A.D., 1999. Life-long history of injuries related to seizures. Epilepsy Res. 34, 123–127.
Persson, H.B., Alberts, K.A., Farahmand, B.Y., Tomson, T., 2002. Risk of extremity fractures in adult outpatients with epilepsy. Epilepsia 43, 768–772.
Ryvlin, P., Werhahn, K.J., Blaszczyk, B., Johnson, M.E., Lu, S., 2014. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia 55, 47–56.
Shetty, P.H., Naik, R.K., Saroja, A., Punith, K., 2011. Quality of life in patients with epilepsy in India. J. Neurosci. Rural Pract. 2, 33–38.
Shorvon, S., Tomson, T., 2011. Sudden unexpected death in epilepsy. Lancet 378, 2028–2038.
Smith, D.F., Baker, G.A., Dewey, M., Jacoby, A., Chadwick, D.W., 1991. Seizure frequency, patient-perceived seizure severity and the psychosocial consequences of intractable epilepsy. Epilepsy Res. 9, 231–241.
Sperling, M.R., Rosenow, F., Faught, E., Hebert, D., Doty, P., Isojarvi, J., 2014. Efficacy of lacosamide by focal seizure subtype. Epilepsy Res. 108, 1392–1398.
Sperling, M.R., Barshow, S., Nei, M., Asadi-Pooya, A.A., 2016. A reappraisal of mortality after epilepsy surgery. Neurology, in press.
Thompson, P.J., Duncan, J.S., 2005. Cognitive decline in severe intractable epilepsy. Epilepsia 46, 1780–1787.
Viteva, E.I., 2014. Seizure frequency and severity: how really important are they for the quality of life of patients with refractory epilepsy. Ann. Indian Acad. Neurol. 17, 35–42.
Walczak, T.S., Leppik, I.E., D'Amelio, M., Rarick, J., So, E., Ahman, P., Ruggles, K., Cascino, G.D., Annegers, J.F., Hauser, W.A., 2001. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology 56, 519–525.
Witt, J.A., Helmstaedter, C., 2012. Should cognition be screened in new-onset epilepsies? A study in 247 untreated patients. J. Neurol. 259, 1727–1731.