Efficacy, safety, and tolerability of brivaracetam with concomitant lamotrigine or concomitant topiramate in pooled Phase III randomized, double-blind trials: A post-hoc analysis

Selim Benbadis [a,*], Pavel Klein [b], Jimmy Schiemann [c,1], Anyzeila Diaz [d], Sami Elmoufti [c], John Whitesides [c]

[a] Comprehensive Epilepsy Program, University of South Florida, Tampa, FL, USA
[b] Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD, USA
[c] UCB Pharma, Raleigh, NC, USA
[d] UCB Pharma, Smyrna, GA, USA

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ABSTRACT

Objective: The objective was to assess the efficacy and safety of adjunctive brivaracetam (BRV) with concomitant use of lamotrigine (LTG) or topiramate (TPM) in patients with uncontrolled focal seizures.
Methods: Data were pooled from three randomized, placebo-controlled Phase III studies (NCT00490035/N01252, NCT00464269/N01253, NCT01261325/N01358) of adults with focal (partial-onset) seizures. Patients taking concomitant levetiracetam were excluded from the efficacy populations, but included in the safety populations. This post-hoc analysis reports data from patients taking BRV in the approved therapeutic range (50–200 mg/day) concomitantly with LTG or TPM.
Results: The number of patients in each of the three BRV dosage groups was small, particularly for the TPM subgroup. Mean percent reduction over placebo in baseline-adjusted focal seizure frequency/28 days for BRV 50, 100, and 200 mg/day was 8.7, 5.3, and 8.9 in the LTG subgroup (n = 220), and 8.4, 21.3, and −4.2 in the TPM subgroup (n = 122). The ≥50% responder rate with concomitant LTG or TPM with BRV 50, 100, and 200 mg/day or placebo was LTG: 28.1%, 36.1%, 34.1%, and 29.1%; and TPM: 14.3%, 44.4%, 25.0%, and 17.5%. There were numerically ≥50%, ≥75%, ≥90%, and 100% responder rates for patients taking BRV ≥50 mg/day compared with placebo in both subgroups. In the LTG and TPM safety populations (n = 245 versus n = 125), treatment-emergent adverse events (TEAEs) were reported with LTG 68.7% versus 68.4%, and TPM 65.6% versus 57.8% (BRV ≥50 mg/day versus placebo). Discontinuations due to TEAEs versus placebo were LTG 7.3% versus 6.3% and TPM 8.2% versus 4.7%. The three most frequently reported TEAEs for both subgroups were somnolence, dizziness, and fatigue. Of these, the incidence of fatigue in the LTG population appeared to increase with dose.
Significance: In this post-hoc pooled analysis, BRV administered with concomitant LTG or TPM reduced seizure frequency and was generally well tolerated for BRV doses of 50–200 mg/day.

1. Introduction

Brivaracetam (BRV) is a selective, high-affinity ligand for synaptic vesicle protein 2A (SV2A). It is approved in North America and many European countries as an adjunctive therapy for focal (partial-onset) seizures in adults (≥16 years, or ≥18 years in Canada and Switzerland). Approval was based on three randomized, placebo-controlled Phase III pivotal studies in patients with refractory focal seizures taking one to two concomitant antiepileptic drugs (AEDs) [1–3]. Pooled analysis of these studies has confirmed that adjunctive BRV is effective and generally well tolerated in adults with focal seizures [4].

In the Phase III studies, BRV was taken in combination with other AEDs. Lamotrigine (LTG), and topiramate (TPM) were frequently coadministered with BRV, and were taken by 24.9% and 11.5% of all patients in these studies, respectively [4]. Carbamazepine (CBZ) was also frequently taken concomitantly, and the results from the subgroup analysis of coadministration of CBZ with BRV will be described in a separate publication (manuscript under submission). The BRV may therefore be expected to be frequently combined with LTG or TPM in clinical practice. The BRV targets the SV2A protein, but both LTG and

TPM have different mechanisms of action. The blockade of voltage-gated sodium channels (VGSC) is the primary mechanism of action for LTG [5], while several mechanisms of action have been proposed for TPM, including carbonic anhydrase inhibition, increased potassium conductance, kainate-type glutamate receptor inhibition, reduction of L-type voltage-sensitive calcium currents, increased frequency of gamma-aminobutyric acid (GABA)-mediated chloride channel opening, and VGSC blockade [5,6].

An awareness of a drug's mechanism of action is important when combining AEDs, as patients are potentially exposed to drug–drug interactions which can be associated with adverse events (AEs). For example, combining drugs that block voltage-dependent sodium channels is more likely to produce neurotoxic side effects, such as dizziness, diplopia, nausea, and ataxia [7–9]. There are claims that the practice of combining AEDs with different mechanisms of action (also known as rational polytherapy), may improve treatment efficacy and tolerability [10,11]. However, clinical studies and real-world evidence in support of rational polytherapy are sparse [11]. Evaluation of the pharmacokinetics of BRV in relation to other AEDs in adults, including LTG and TPM, has shown no evidence of any drug–drug interactions [12]. However, when introducing a new AED, such as BRV, to an existing regimen, it is important to consider the efficacy and safety in patients taking these specific concomitant AEDs. This post-hoc subgroup analysis was conducted to assess efficacy, safety, and tolerability of BRV with concomitant LTG or TPM.

2. Methods

2.1. Study population

This was a post-hoc analysis of data pooled from three randomized, double-blind, placebo-controlled, fixed-dose Phase III studies in adult patients with epilepsy (N01253 [NCT00464269; BRV 5, 20, and 50 mg/day], N01252 [NCT00490035; BRV 20, 50, and 100 mg/day], and N01358 [NCT01261325; BRV 100 and 200 mg/day]) [1–3]. The methodologies, as well as inclusion and exclusion criteria of the enrolled patients in the composite studies, have been described in detail previously [1–3]. Patients enrolled in the studies were 16–80 years of age with uncontrolled, well-categorized focal seizures, with or without secondary generalization, despite treatment with one to two concomitant AEDs. In all studies, BRV was initiated without uptitration. All studies were conducted in accordance with the International Conference on Harmonization notes for Guidance on Good Clinical Practice and the Declaration of Helsinki. The study protocols were approved by institutional review boards at all study sites, and all patients (or their legal guardians) provided written informed consent prior to participation.

For the original pooled analysis, the population was restricted to patients taking approved doses of BRV 50, 100, or 200 mg/day, or placebo, and patients taking concomitant levetiracetam (LEV) were excluded from the efficacy population [4]. The safety population included all patients who took ≥1 dose of study drug, including those taking concomitant LEV. The patient groups for the post-hoc analysis reported here comprised patients from the pooled efficacy and safety populations who were receiving concomitant LTG or TPM. Patients taking concomitant TPM were excluded from the LTG subgroup, and vice versa.

2.2. Endpoints

In the original Phase III studies, seizure types were classified according to the International League Against Epilepsy (ILAE) 1981 guidelines [13]. For the purposes of the pooled analysis, seizure types were not recoded according to the updated ILAE terminology [14,15]. We have therefore used "focal seizures" throughout this manuscript to describe all subtypes of partial-onset (focal) seizures, except where we refer to the patients' specific baseline seizure types.

To facilitate comparison with the overall pooled population, we used the same primary efficacy outcomes in this post-hoc analysis as in the original pooled analysis. Therefore, the efficacy endpoints for this analysis were percent reduction in focal seizure frequency over placebo per 28 days and ≥50% responder rate. In addition to these primary outcomes, the ≥75%, ≥90%, and 100% responder rates were also calculated. Safety outcomes included the incidence of treatment-emergent adverse events (TEAEs), severe TEAEs, and patient withdrawal due to TEAEs.

2.3. Statistical analysis

Percent reduction in focal seizure frequency over placebo per 28 days was assessed by analysis of covariance with log-transformed treatment period 28-day adjusted focal seizure frequency as the outcome and an effect for treatment, study, and log-transformed baseline focal seizure frequency as a continuous covariate. Responder rate (≥50%, ≥75%, ≥90%, and 100%) treatment group comparisons were based on a logistic regression model with ≥50%, ≥75%, ≥90%, and 100% responder outcome, respectively, for treatment period 28-day adjusted focal seizure frequency as the outcome, with effects for treatment, study and log-transformed baseline focal seizure frequency as a continuous covariate. Note that these standard responder rate calculations were based on the available seizure diary data and included patients who discontinued, therefore, the 100% responder rate is not directly equivalent to seizure freedom. For some of the outcomes, the small patient numbers meant that the model fit was poor and so p-values were not calculated. This was a post-hoc analysis and a threshold α value for statistical significance was not defined. All reported p-values can therefore only be interpreted in an exploratory manner.

3. Results

3.1. Patient disposition and demographics

The efficacy population comprised 220 patients in the LTG subgroup and 122 patients in the TPM subgroup. The safety population comprised 245 patients in the LTG subgroup and 125 patients in the TPM subgroup. The number of patients in each of the BRV dosage groups was small, particularly for the TPM subgroup (Table 1).

Patient demographics and baseline epilepsy characteristics were similar across most treatment groups, with some exceptions. Among patients taking BRV, the TPM subgroup had fewer male patients (28.8%) and more Asian patients (22.0%) compared with the LTG group (44.8% and 5.2%, respectively) (Table 1). Although patients were stratified for LEV use at study entry, both the LTG- and the TPM-pooled subgroups were skewed toward LEV-naive status at BRV 50 mg/day and toward prior LEV exposure at BRV 200 mg/day.

Across the LTG and TPM subgroups, the mean duration of epilepsy ranged from 21.6 to 25.7 years and the majority of patients reported Type IB (complex partial) seizures during the baseline period. The majority of patients in both subgroups were taking an additional concomitant AED (LTG: 95.5% and TPM: 95.1%) as well as study treatment (BRV or placebo) and LTG or TPM. In both subgroups, similar proportions of patients had tried and discontinued ≥2 AEDs (83.2% in the LTG subgroup, 82.8% in the TPM subgroup), which was comparable to the overall pooled population (75.7%) [4].

3.2. Efficacy

Comparisons of LTG versus TPM for 28-day adjusted reduction in seizure frequency over placebo by BRV dose (Fig. 1) showed a variable pattern of seizure reduction. The TPM subgroup had a particularly high response with BRV 100 mg/day, while overall (BRV 50–200 mg/day), patients taking BRV with either concomitant TPM or LTG attained

Table 1
Patient demographics and disease characteristics (efficacy population).

	LTG subgroup, n = 220					TPM subgroup, n = 122				
	Placebo (n = 86)	BRV 50 mg/day (n = 32)	BRV 100 mg/day (n = 61)	BRV 200 mg/day (n = 41)	BRV overall[a] (n = 134)	Placebo (n = 63)	BRV 50 mg/day (n = 7)	BRV 100 mg/day (n = 36)	BRV 200 mg/day (n = 16)	BRV overall[a] (n = 59)
Age, years, mean (SD)	37.6 (12.6)	35.9 (11.6)	36.8 (11.4)	38.6 (11.4)	37.1 (11.4)	39.3 (10.8)	32.4 (14.1)	36.7 (11.2)	32.6 (9.0)	35.1 (11.0)
Male, n (%)	39 (45.3)	13 (40.6)	27 (44.3)	20 (48.8)	60 (44.8)	29 (46.0)	2 (28.6)	7 (19.4)	8 (50.0)	17 (28.8)
Ethnicity, n (%)										
White[b]	65 (75.6)	23 (71.9)	53 (86.9)	30 (73.2)	106 (79.1)	51 (81.0)	5 (71.4)	25 (69.4)	11 (68.8)	41 (69.5)
Black	4 (4.7)	1 (3.1)	1 (1.6)	1 (2.4)	3 (2.2)	3 (4.8)	0	1 (2.8)	1 (6.3)	2 (3.4)
Asian	7 (8.1)	4 (12.5)	1 (1.6)	2 (4.9)	7 (5.2)	8 (12.7)	0	9 (25.0)	4 (25.0)	13 (22.0)
Other	10 (11.6)	4 (12.5)	6 (9.8)	8 (19.5)	18 (13.4)	1 (1.6)	2 (28.6)	0	0	2 (3.4)
Missing	0	0	0	0	0	0	0	1 (2.8)	0	1 (1.7)
Regions, n (%)										
North America	21 (24.4)	6 (18.8)	15 (24.6)	16 (39.0)	37 (27.6)	14 (22.2)	2 (28.6)	3 (8.3)	4 (25.0)	9 (15.3)
Latin America	17 (19.8)	6 (18.8)	6 (9.8)	6 (14.6)	18 (13.4)	4 (6.3)	4 (57.1)	1 (2.8)	0	5 (8.5)
Western Europe	14 (16.3)	8 (25.0)	17 (27.9)	10 (24.4)	35 (26.1)	12 (19.0)	0	9 (25.0)	2 (12.5)	11 (18.6)
Eastern Europe	25 (29.1)	5 (15.6)	22 (36.1)	7 (17.1)	34 (25.4)	22 (34.9)	1 (14.3)	14 (38.9)	6 (37.5)	21 (35.6)
Asia/Pacific/other	9 (10.5)	7 (21.9)	1 (1.6)	2 (4.9)	10 (7.5)	11 (17.5)	0	9 (25.0)	4 (25.0)	13 (22.0)
Weight, kg, mean (SD)	78.3 (19.7)	69.8 (14.3)	73.8 (15.4)	74.9 (19.6)	73.2 (16.5)	74.4 (21.7)	61.1 (12.6)	70.3 (18.6)	69.8 (15.5)	69.1 (17.2)
Age at time of first seizure, years, mean (SD)	15.6 (12.4)	10.7 (11.0)	15.7 (11.7)	14.4 (12.8)	14.1 (12.0)	14.8 (13.7)	8.4 (6.1)	12.5 (10.9)	10.8 (7.2)	11.5 (9.6)
LEV status										
Previous LEV only	40 (46.5)	10 (31.3)	28 (45.9)	26 (63.4)	64 (47.8)	28 (44.4)	1 (14.3)	20 (55.6)	11 (68.8)	32 (54.2)
Never used LEV	46 (53.5)	22 (68.8)	33 (54.1)	15 (36.6)	70 (52.2)	35 (55.6)	6 (85.7)	16 (44.4)	5 (31.3)	27 (45.8)
Number of concomitant AEDs[c]										
1	83 (96.5)	28 (87.5)	58 (95.1)	41 (100)	127 (94.8)	58 (92.1)	7 (100)	35 (97.2)	16 (100)	58 (98.3)
≥2	3 (3.5)	4 (12.5)	3 (4.9)	0	7 (5.2)	5 (7.9)	0	1 (2.8)	0	1 (1.7)
AED inducer status										
No inducer at core study entry	46 (53.5)	16 (50.0)	34 (55.7)	26 (63.4)	76 (56.7)	17 (27.0)	1 (14.3)	11 (30.6)	10 (62.5)	22 (37.3)
No. of prior AEDs[d]										
0–1	15 (17.4)	7 (21.9)	10 (16.4)	5 (12.2)	22 (16.4)	11 (17.5)	3 (42.9)	3 (8.3)	4 (25.0)	10 (16.9)
2–4	30 (34.9)	18 (56.3)	21 (34.4)	15 (36.6)	54 (40.3)	29 (46.0)	4 (57.1)	16 (44.4)	4 (25.0)	24 (40.7)
≥5	41 (47.7)	7 (21.9)	30 (49.2)	21 (51.2)	58 (43.3)	23 (36.5)	0	17 (47.2)	8 (50.0)	25 (42.4)
Seizure types reported during baseline[e]										
Type IA	39 (45.3)	11 (34.4)	26 (42.6)	16 (39.0)	53 (39.6)	26 (41.3)	3 (42.9)	10 (27.8)	4 (25.0)	17 (28.8)
Type IB	71 (82.6)	28 (87.5)	51 (83.6)	35 (85.4)	114 (85.1)	52 (82.5)	7 (100)	33 (91.7)	14 (87.5)	54 (91.5)
Type IC	8 (20.9)	16 (50.0)	15 (24.6)	13 (31.7)	44 (32.8)	22 (34.9)	3 (42.9)	13 (36.1)	5 (31.3)	21 (35.6)

AED, antiepileptic drug; BRV, brivaracetam; ILAE 1981, International League Against Epilepsy 1981; LEV, levetiracetam; LTG, lamotrigine; SD, standard deviation; TPM, topiramate.

[a] BRV overall = BRV 50, 100, and 200 mg/day combined.

[b] Includes patients described as White, Caucasian, or Hispanic, because of differences in recording racial groups across the three studies.

[c] Number of concomitant AEDs excluding LTG and TPM.

[d] Previous AEDs that were discontinued prior to study entry. N01252 and N01253 collected AED use within 5 years prior to study entry, whereas, N01358 collected all history of AEDs prior to study entry.

[e] Baseline seizure types are reported according to their ILAE 1981 classifications in the original Phase III studies: Type IA, simple partial-onset; Type IB, complex partial-onset; Type IC, partial-onset evolving to secondary generalized.

similar seizure reduction. However, it should be noted that these were small patient numbers, particularly in the TPM subgroup, and this was reflected by wide confidence intervals for this endpoint (data not shown).

Numerically ≥50% responder rates for patients taking concomitant LTG or TPM were seen in patients in the BRV 100 and 200 mg/day groups compared with placebo (Fig. 2). Again, the TPM subgroup had a particularly high response at BRV 100 mg/day, and comparisons of LTG versus TPM showed a variable pattern of seizure reduction. Similarly, the ≥50%, ≥75%, ≥90%, and 100% responder rates for all patients taking BRV were numerically greater for patients taking concomitant LTG (Fig. 3A) or TPM (Fig. 3B) compared with placebo. In the LTG subgroup, the separation from placebo appears to increase at higher responder rates (Fig. 3A). Comparisons of LTG versus TPM show similar levels of seizure reduction (Fig. 3A and B).

3.3. Safety and tolerability

The incidence of TEAEs in the LTG subgroup was similar across the BRV dosage groups compared with placebo (Table 2). Conversely, the incidence of TEAEs in the TPM subgroup was higher in the BRV dosage groups compared with placebo, although there was no clear dose response (Table 3). Among all patients taking BRV, both subgroups had a similar incidence of TEAEs (68.7% in the LTG subgroup, 65.6% in

the TPM subgroup), and discontinuations due to TEAEs (7.3% in the LTG subgroup, 8.2% in the TPM subgroup), which were both similar to the corresponding placebo rates (Tables 2 and 3).

Across the BRV dosage groups, the incidence of drug-related TEAEs (as assessed by the investigator) and severe TEAEs were higher in the BRV dosage groups versus placebo in both the LTG and TPM subgroups. However, there was no clear dose response in the TPM subgroup. Three patients on BRV in the LTG subgroup and one patient on BRV in the TPM subgroup reported a serious TEAE that was considered related to study medication. One death, which was recorded as brain hypoxia, and met criteria for sudden unexpected death in epilepsy (SUDEP), was reported in a patient taking BRV 50 mg/day and LTG, as previously described [4]. The TEAEs most frequently reported by all patients taking BRV were somnolence, dizziness, and fatigue, which were the same for both the LTG and TPM subgroups (Tables 2 and 3). The rates of the most common psychiatric TEAEs (irritability, depression, anxiety, and insomnia) were similar for the LTG and TPM groups (data not shown, incidence was <3% of BRV patients overall except for anxiety in the LTG subgroup) and did not differ markedly from the overall safety patient population [4].

4. Discussion

The results of this post-hoc analysis indicate that adjunctive treatment with BRV ranging from 50 to 200 mg/day without titration was
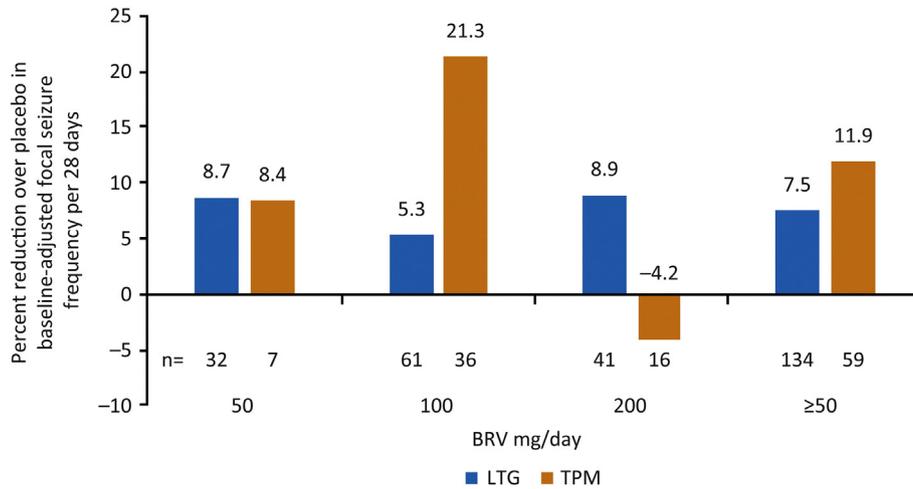
Fig. 1. Percent reduction over placebo in baseline-adjusted focal seizure frequency per 28 days for patients taking brivaracetam with lamotrigine or topiramate (efficacy population). BRV, brivaracetam; LTG, lamotrigine; TPM, topiramate.

generally well tolerated in patients with focal seizures taking concomitant LTG or TPM. These safety results are similar to the pooled data from three randomized, double-blind, placebo-controlled, fixed-dose Phase III studies in patients with epilepsy [4].

As BRV and LEV both exert their antiepileptic effects via SV2A, patients were stratified for LEV use at study entry. Both the LTG- and the TPM-pooled subgroups were skewed toward LEV-naive status at BRV 50 mg/day and toward prior LEV exposure at BRV 200 mg/day. A likely explanation for this skew is that it is due to the exclusion of patients taking concomitant LEV in studies N01252 and N01253 from the pooled efficacy population. Study N01358 did not permit concomitant LEV, and was also the only study to use the 200 mg/day BRV dosage, hence, the higher proportion of prior LEV exposures at this BRV dosage.

Patients treated with BRV 100 or 200 mg/day, and either TPM or LTG, appeared more likely to achieve a ≥50% reduction in seizure frequency compared with the corresponding placebo groups. The ≥50% responder rates for patients taking BRV 200 mg/day with concomitant LTG were 34.1% and 25.0% for those taking concomitant TPM, compared with 38.7% in the overall pooled population in the pivotal studies. Furthermore, ≥50%, ≥75%, ≥90%, and 100% responder rates were numerically greater in the overall BRV group (50–200 mg/day) compared with placebo in both LTG and TPM subgroups. Conversely, percent

reduction over placebo in baseline-adjusted focal seizure frequency per 28 days in this analysis was not substantially increased in those taking BRV 50–200 mg/day versus placebo in either subgroup (7.5% for the LTG subgroup and 11.9% for the TPM subgroup), unlike in the overall pooled BRV population in the pivotal studies, which attained a 24% reduction. Comparisons of LTG versus TPM for all efficacy outcomes show variable patterns of seizure reduction with wide confidence intervals, which can be explained by the small patient numbers, particularly in the TPM subgroup.

The incidences of TEAEs in the LTG and TPM subgroups are also similar to those previously reported in the overall pooled population [4]. The incidence of dizziness and fatigue with concomitant LTG appear disproportionately high with BRV 200 mg/day. However, this high number is accentuated by the low incidence of dizziness and fatigue with BRV 100 mg/day in comparison with BRV 50 mg/day and placebo. It should also be noted that dizziness and fatigue both increased with BRV dose in the overall pooled population [4], and the notably higher incidence of dizziness in the LTG subgroup, as opposed to the TPM subgroup, could be attributed to noise resulting from the small patient numbers.

In the Phase III trials, BRV was commonly taken with LTG or TPM. It can therefore be expected that BRV will potentially be coadministered with these AEDs in clinical practice. The LTG and TPM are among the
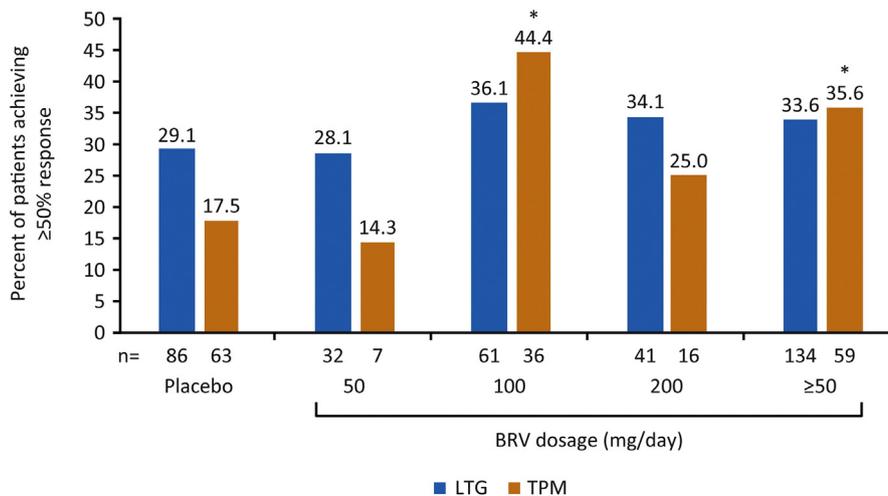

Fig. 2. The ≥50% responder rate for patients taking brivaracetam with lamotrigine or topiramate (efficacy population). *p < 0.05. BRV, brivaracetam; LTG, lamotrigine; TPM, topiramate.
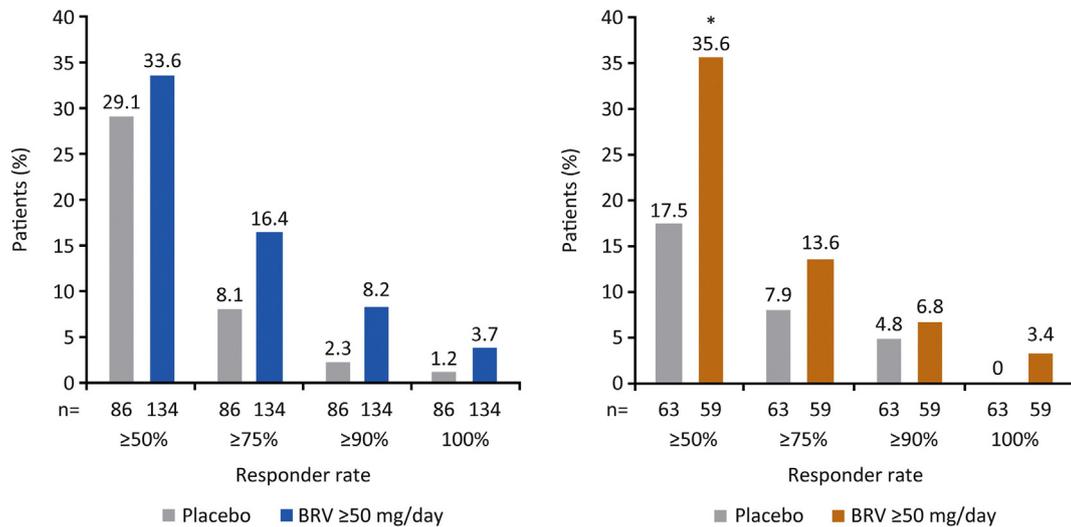
Fig. 3. The ≥50%, ≥75%, ≥90%, and 100% responder rates for patients taking (A) lamotrigine or (B) topiramate with brivaracetam ≥50 mg/day or placebo (efficacy population). *p < 0.05. BRV, brivaracetam.

most frequently prescribed AEDs in patients with focal seizures, and have a different mechanism of action to BRV. Findings by Margolis and colleagues suggest that AED combinations with different mechanisms of action result in greater treatment persistence, and lower risks for hospitalization and emergency department visits, than when combination therapy utilizes those with similar mechanisms of action [10]. Additionally, combinations with LTG and valproate have produced a favorable response [7,9]. However, there are as yet no randomized clinical studies, and population-level or real-world evidence to support that the use of rational polytherapy is sparse [11]. Based on the hypothesis that mechanistically-unrelated AEDs may have a synergistic effect when used in combination, this did not appear to be the case when BRV was combined with LTG or TPM. However, due to the low patient numbers in the respective subgroups, no definite conclusion can be drawn. Safety results indicate that BRV was generally well tolerated when administered concomitantly with LTG or TPM, as the incidence of TEAEs and discontinuations from TEAEs was similar to the original pooled analysis. Results from this analysis will add to an improved understanding of the safety of BRV in patients taking other commonly prescribed AEDs.

The main limitation of this study was the small patient samples in each dosage subgroup. This is a post-hoc analysis of pooled data from three Phase III trials examining the efficacy of BRV in patients with epilepsy taking one to two concomitant AEDs, and the individual studies

did not recruit patients specifically taking concomitant LTG or TPM. All patients in this post-hoc analysis were taking at least one other concomitant AED other than LTG or TPM. This analysis was therefore exploratory in nature and, as such, was not powered to detect statistically significant differences in the efficacy or safety of BRV with concomitant LTG or TPM. With a larger overall sample size of patients taking concomitant LTG or TPM, it is possible that the observed trends in percent reduction over placebo in baseline-adjusted focal seizure frequency, and responder rates in those receiving therapeutic doses of BRV would have reached statistical significance. An additional limitation is that the original Phase III studies did not record the doses of concomitant LTG and TPM taken by the participants, or indeed of any concomitant AED. The recommended dose of TPM for adults with focal seizures is 200–400 mg/day [16], while LTG dosing is based on concomitant medications, and can vary between 100 and 500 mg/day [17]. It is possible that the doses of LTG and TPM taken during the BRV Phase III studies could have influenced the response.

This post-hoc analysis supports the safety and tolerability of adjunctive BRV taken with concomitant LTG or TPM. Although efficacy results of LTG versus TPM when combined with BRV showed generally similar levels of seizure reduction, it is not possible to draw any conclusions on the effect of these concomitant AEDs on BRV efficacy as low patient numbers produced variable results. An awareness of these common AED combinations is critical, and further analyses based on

Table 2

Summary and incidence of treatment-emergent adverse events reported in ≥3% of patients taking brivaracetam or placebo with lamotrigine (safety population; n = 245).

n (%)	Placebo (n = 95)	BRV 50 mg/day (n = 44)	BRV 100 mg/day (n = 65)	BRV 200 mg/day (n = 41)	BRV overall[a] (n = 150)
Any TEAE	65 (68.4)	33 (75.0)	40 (61.5)	30 (73.2)	103 (68.7)
Discontinuation because of TEAE	6 (6.3)	2 (4.5)	5 (7.7)	4 (9.8)	11 (7.3)
Drug-related TEAEs	29 (30.5)	20 (45.5)	22 (33.8)	22 (53.7)	64 (42.7)
Severe TEAEs	3 (3.2)	2 (4.5)	3 (4.6)	4 (9.8)	9 (6.0)
Serious TEAEs	2 (2.1)	2 (4.5)	1 (1.5)	2 (4.9)	5 (3.3)
Drug-related serious TEAEs	1 (1.1)	1 (2.3)	0	2 (4.9)	3 (2.0)
Deaths	0	1 (2.3)	0	0	1 (0.7)
TEAEs reported in ≥ 3% of BRV-treated patients overall					
Somnolence	9 (9.5)	7 (15.9)	9 (13.8)	5 (12.2)	21 (14.0)
Dizziness	8 (8.4)	7 (15.9)	2 (3.1)	12 (29.3)	21 (14.0)
Fatigue	1 (1.1)	2 (4.5)	3 (4.6)	9 (22.0)	14 (9.3)
Headache	10 (10.5)	5 (11.4)	3 (4.6)	4 (9.8)	12 (8.0)
Vomiting	1 (1.1)	4 (9.1)	2 (3.1)	2 (4.9)	8 (5.3)
Anxiety	4 (4.2)	1 (2.3)	2 (3.1)	3 (7.3)	6 (4.0)

BRV, brivaracetam; TEAE, treatment-emergent adverse event.

[a] BRV overall = BRV 50, 100, and 200 mg/day combined.

Table 3
Summary and incidence of treatment-emergent adverse events reported in ≥3% of patients taking brivaracetam or placebo with topiramate (safety population; n = 125).

n (%)	Placebo (n = 64)	BRV 50 mg/day (n = 9)	BRV 100 mg/day (n = 36)	BRV 200 mg/day (n = 16)	BRV overall[a] (n = 61)
Any TEAE	37 (57.8)	7 (77.8)	22 (61.1)	11 (68.8)	40 (65.6)
Discontinuation because of TEAE	3 (4.7)	0	4 (11.1)	1 (6.3)	5 (8.2)
Drug-related TEAEs	21 (32.8)	6 (66.7)	15 (41.7)	8 (50.0)	29 (47.5)
Severe TEAEs	3 (4.7)	1 (11.1)	2 (5.6)	2 (12.5)	5 (8.2)
Serious TEAEs	2 (3.1)	0	1 (2.8)	1 (6.3)	2 (3.3)
Drug-related serious TEAEs	0	0	1 (2.8)	0	1 (1.6)
Deaths	0	0	0	0	0
TEAEs reported in ≥ 3% of BRV-treated patients overall					
Somnolence	7 (10.9)	3 (33.3)	7 (19.4)	3 (18.8)	13 (21.3)
Dizziness	6 (9.4)	1 (11.1)	3 (8.3)	3 (18.8)	7 (11.5)
Fatigue	3 (4.7)	0	4 (11.1)	2 (12.5)	6 (9.8)
Upper respiratory tract infection	3 (4.7)	0	2 (5.6)	1 (6.3)	3 (4.9)
Insomnia	1 (1.6)	1 (11.1)	2 (5.6)	0	3 (4.9)
Cough	0	0	2 (5.6)	1 (6.3)	3 (4.9)
Irritability	0	1 (11.1)	1 (2.8)	0	2 (3.3)
Nasopharyngitis	2 (3.1)	0	2 (5.6)	0	2 (3.3)
Headache	6 (9.4)	2 (22.2)	0	0	2 (3.3)
Depression	2 (3.1)	0	1 (2.8)	1 (6.3)	2 (3.3)
Oropharyngeal pain	1 (1.6)	1 (11.1)	1 (2.8)	0	2 (3.3)
Rhinorrhea	0	0	2 (5.6)	0	2 (3.3)

BRV, brivaracetam; TEAE, treatment-emergent adverse event.
  [a] BRV overall = BRV 50, 100, and 200 mg/day combined.

real-world data from clinical practice will permit a better understanding of the efficacy and safety in patients taking BRV with other specific AEDs.

Disclosure of conflicts of interest

Dr. Benbadis has served as a consultant for Acorda, Cyberonics, Eisai, Lundbeck, Sunovion, UCB Pharma, and Upsher-Smith, and is on the speakers bureaux for Cyberonics (Livanova), Eisai, Glaxo Smith Kline, Lundbeck, Sunovion, and UCB Pharma. He has received grant support from Acorda, Cyberonics, GW, Lundbeck, Sepracor, Sunovion, UCB Pharma, and Upsher-Smith. Dr. Whitesides, Dr. Diaz, and Mr. Elmoufti are employees of UCB Pharma. Dr. Klein has served as a consultant for Eisai, Lundbeck, Sunovion, and UCB Pharma, and is on the speakers bureaux for Eisai, Sunovion, and UCB Pharma. He has received grant support from Eisai and Lundbeck. Dr. Schiemann was an employee of UCB Pharma at the time when the original studies were conducted and is a current employee of Teva Pharmaceuticals.

Qualified researchers whose proposed use of the data has been approved by an independent review panel will be given access to anonymized individual participant data and redacted study documents. Additional information is available on www.ClinicalStudyDataRequest. com.

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