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Safety, tolerability, and efficacy of brivaracetam as adjunctive therapy in patients with focal seizures, generalized onset seizures, or Unverricht–Lundborg disease: An open-label, long-term follow-up trial

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ABSTRACT

This long-term open-label extension (OLE) trial was conducted to evaluate the long-term safety and tolerability of brivaracetam (BRV) at individualized doses in patients with epilepsy and focal (partial-onset) or generalized onset seizures, or Unverricht–Lundborg disease (ULD). A secondary objective was to evaluate efficacy of BRV in the subgroups of patients with focal or generalized onset seizures.

Patients with epilepsy were eligible to enroll in this OLE (N01125; NCT00175916) and were analyzed if they had completed a previous double-blind BRV trial (N01114 [NCT00175929], N01252 [NCT00490035], N01254 [NCT00504881], N01187 [NCT00357669], and N01236 [NCT00368251]), and were expected to obtain a reasonable benefit from long-term BRV treatment. Patients entered the OLE at the BRV dose recommended at the end of the previous trial, with dose adjustments of BRV and concomitant antiseizure medications permitted. Safety variables included treatment-emergent adverse events (TEAEs). Efficacy variables in patients with focal seizures were percent reduction in focal seizure frequency, 50 % responder rates, and 6- and 12-month seizure-freedom. Eight hundred and fifty-three patients (729 [85.5 %] with focal seizures, 30 [3.5 %] with generalized onset seizures, and 94 [11.0 %] with ULD) were enrolled and included in the Safety Set. Overall, 619 (72.6 %) patients discontinued the trial, mainly due to lack of efficacy (354 [41.5 %]), adverse events (100 [11.7 %]), and patient choice (98 [11.5 %]). During the OLE, 588 (68.9 %) patients received BRV for ≥12 months, 403 (47.2 %) for ≥36 months, and 223 (26.1 %) for ≥96 months. The most common modal dose of BRV was 150 mg/day (415 [48.7 %] patients). In the ULD subgroup, the most common modal BRV dose was 100 mg/day (44/94 [46.8 %] patients), and 37/94 (39.4 %) patients had ≥96 months of BRV exposure. Overall, 720/853 (84.4 %) patients reported TEAEs, 451 (52.9 %) had a drug-related TEAE, and 95 (11.1 %) discontinued BRV due to a TEAE. In the ULD subgroup, 87/94 (92.6 %) patients reported TEAEs, 60 (63.8 %) had a drug-related TEAE, and 16 (17.0 %) discontinued due to a TEAE. In patients with focal seizures, the median reduction in focal seizure frequency from Baseline was 43.1 % ($n = 728$), the 50 % responder rate was 43.6 % ($n = 729$), and 6- and 12-month seizure freedom rates were 22.2 % and 15.8 %, respectively ($n = 595$).

Overall, BRV was well-tolerated as long-term adjunctive therapy in patients with focal seizures, generalized onset seizures, or Unverricht–Lundborg disease, with improvements in focal seizure frequency maintained over time.

Abbreviations: AE, adverse event; ASM, antiseizure medication; BRV, brivaracetam; EQ-5D, EuroQol-5 Dimensions Questionnaire; ES, Efficacy Set; HADS, Hospital Anxiety and Depression Scale; ILAE, International League Against Epilepsy; LEV, levetiracetam; OLE, open-label extension; QOLIE-31-P, Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; SD, standard deviation; SS, Safety Set; SV2A, synaptic vesicle protein 2A; TEAE, treatment-emergent adverse event; ULD, Unverricht–Lundborg disease.

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1. Introduction

Brivaracetam (BRV) is an antiseizure medication (ASM) with high and selective interaction with the synaptic vesicle protein 2A (SV2A) in the brain (Gillard et al., 2011; Matagne et al., 2008). In Europe and Australia, BRV is indicated for adjunctive therapy in patients ≥4 years of age with focal (partial-onset) seizures (with or without secondary generalization) (UCB Pharma, 2019a,b; UCB Pharma, 2020), and in the United States as adjunctive therapy and monotherapy in patients ≥4 years of age with focal seizures (oral formulations only; BRV injection is indicated for patients ≥16 years of age) (UCB Inc, 2018). The recommended dosage of BRV for adults (16 years and older) is 50–200 mg/day, with a recommended starting dosage of 100 mg/day.

Safety, tolerability, and efficacy of adjunctive BRV as treatment for focal seizures has been confirmed by pooled data of Phase IIb/III and long-term follow-up trials (≥8.0 years) (Toledo et al., 2016). For generalized onset seizures, exploratory results from a small group of patients in one trial suggested that the tolerability of BRV did not appear different from that of patients with focal seizures, and that BRV may be efficacious in these patients (Kwan et al., 2014).

Two double-blind Phase III trials were conducted to evaluate the efficacy, tolerability, and safety of adjunctive BRV in patients with Unverricht–Lundborg disease (ULD) (Kälviäinen et al., 2016), a rare, progressive epilepsy disorder characterized by generalized onset epileptic seizures and severe stimulus-sensitive myoclonus (Kälviäinen et al., 2008; Lehesjoki, 2002). These trials did not show a significant improvement in action myoclonus score with BRV. However, BRV was generally well tolerated in patients with ULD.

This open-label extension (OLE) trial was conducted to provide patients who participated in specific BRV trials the opportunity to access continued adjunctive BRV treatment. The primary objective of this OLE trial was to evaluate the long-term safety and tolerability of adjunctive BRV treatment at individualized doses up to 200 mg/day in patients with focal seizures, generalized onset seizures, or ULD. The secondary objective was to evaluate the maintenance of efficacy of BRV over time in patients with focal or generalized onset seizures.

2. Materials and methods

2.1. Trial design

This Phase III, multicenter, single-arm, long-term follow-up, OLE trial (N01125; NCT00175916) enrolled patients with epilepsy (≥16 years) who had participated in a previous BRV trial. Patients enrolled in the initial double-blind BRV trials had focal seizures (entering from trials N01114: NCT00175929 (Van Paesschen et al., 2013); N01252: NCT00490035 (Ryvlin et al., 2014); N01254: NCT00504881 (Kwan et al., 2014)), generalized onset seizures (trial N01254) (Kwan et al., 2014), or ULD with moderate to severe myoclonus (trials N01187: NCT00357669; N01236: NCT00368251) (Kälviäinen et al., 2016) (Table S1). Six patients entered the OLE in Germany upon closure of an open-label BRV Phase III trial (N01315; NCT00761774) (Arnold et al., 2020). This allowed patients to continue to receive BRV in the absence of a managed care program. These patients were excluded from efficacy and safety analyses of this OLE trial (N01125).

Patients were eligible to participate in the OLE if they had completed one of the previous trials and were expected to obtain a reasonable benefit from long-term administration of BRV in the opinion of the investigator. Exclusion criteria included severe medical, neurological, and psychiatric disorders or laboratory values that might have had an impact on the safety of the patient, poor adherence to the visit schedule or medication intake in the previous BRV trial, or participation in any clinical trial of another investigational medicinal product or device during the trial. Women who were pregnant, lactating, or of childbearing potential and not using a medically approved contraceptive method were excluded. Alternatively, sexual abstinence was accepted on a case-by-case basis in all countries except France.

The individual starting dose of BRV was the dose recommended for each patient at the end of the previous trial. The maximum permitted dose was initially BRV 400 mg/day. Following protocol amendments, this was reduced to 150 mg/day on April 01, 2005 and then increased to 200 mg/day on January 03, 2011. Doses of BRV, concomitant ASMs or antimyoclonic drugs could be adjusted at any time during the trial based on the patient's safety, tolerability, and seizure control. Up- or down-titrations of BRV were permitted in increments of 50 mg/day on a weekly basis. Use of concomitant vigabatrin and felbamate was not permitted in any patients during the trial, and use of phenytoin was not permitted in patients with ULD. The individual trial duration was dependent on the patient's access to locally approved commercial BRV. A patient was defined as a completer if they completed the full extent of the trial as defined in the protocol, transitioned to another BRV trial, managed access program or similar type of program, or converted to commercial BRV. Patients who discontinued BRV entered a down-titration period, with a last down titration step at 20 mg/day for one week followed by a period free of BRV for 2–4 weeks before the final visit.

2.2. Variables

Primary safety and tolerability variables were the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, and discontinuations due to adverse events (AEs). TEAEs were defined as AEs that had onset on or after the day of first BRV dose. TEAEs of epilepsy and/or convulsion were reported for patients who had an increase in seizure frequency or intensity, new seizure types, or worsening of seizures. TEAEs potentially associated with behavioral disorders and TEAEs potentially associated with suicidality or suicidal ideation were based on a list of Medical Dictionary for Regulatory Activities preferred terms. Other safety variables included laboratory tests, vital signs, body weight, electrocardiogram, and physical and neurological examinations. Change in Hospital Anxiety and Depression Scale (HADS) scores (Zigmond and Snaith, 1983) was assessed from Baseline of the previous trial to the last value in Year 2 (i.e., the last available score at or before the Year 2 assessment), for patients with focal and generalized onset seizures.

For patients with focal seizures, secondary efficacy variables were focal seizure frequency per 28 days during the Evaluation Period, percent reduction in focal seizure frequency per 28 days from Baseline in the previous trial, 50 % responder rates (patients with a ≥50 % reduction in focal seizure frequency from Baseline), and other efficacy variables were the percentage of patients continuously seizure-free (all seizure types) for at least 6 months and at least 12 months during the Evaluation Period. For patients with generalized onset seizures, other efficacy variables were the same as the efficacy variables for patients with focal seizures; however, days with generalized onset seizures were measured instead of focal seizure frequency. Other variables (evaluated separately for patients with focal seizures and patients with generalized onset seizures) were change in Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) (Cramer et al., 2003) scores and EuroQol-5 Dimensions Questionnaire (EQ-5D) responses from Baseline of the previous trial to the last value in Year 2. No efficacy variables were defined for patients with ULD.

2.3. Statistical analyses

No statistical hypothesis testing was planned and all variables were summarized using descriptive statistics. The Safety Set (SS) comprised all patients who took at least one dose of BRV, excluding those from N01315. All patients in the SS who took at least one dose of trial medication and had at least one seizure Daily Record Card day during the Evaluation Period were included in the Efficacy Set (ES). Separate efficacy populations were defined for patients with focal seizures and

patients with generalized onset seizures.

Patients were classified into completer cohorts based on their minimum exposure to BRV. For example, patients completing at least 12 months of BRV treatment were included in the 12-month completer cohort. A month was defined as 30 days, with time intervals based on monthly durations as multiples of 30 days (e.g., 12 months = 360 days). For assessments of continuous seizure-freedom, patients were defined as seizure-free for 6 and 12 months if they did not report any seizures, and the seizure diary was completed for at least 90 % of days, within the specified time interval. Patients were considered failures for seizure-freedom if their duration of BRV treatment was less than the specified duration of seizure-freedom.

2.4. Post hoc analyses

The percent reduction in focal seizure frequency per 28 days from Baseline in the previous trial, 50 % responder rates, and the percentage of patients continuously seizure-free for at least 6 months and at least 12 months during the Evaluation Period were evaluated in post hoc analyses for patients with focal seizures previously exposed to levetiracetam (LEV) and patients who were LEV-naïve. Previous LEV was defined as LEV taken and discontinued before entry into the previous trial. Patients who started LEV during this trial were excluded.

3. Results

3.1. Patient disposition and Baseline characteristics

This OLE trial was conducted between September 2005 and May 2019, at 156 sites in 26 countries (North and Latin America, Europe, Africa, Asia, and Asia Pacific). A total of 853 patients were enrolled, received at least one dose of BRV, and were included in the SS. Seven hundred and twenty-nine (85.5 %) patients had focal seizures, 30 (3.5 %) patients had generalized onset seizures, and 94 (11.0 %) patients had ULD.

Overall, 234 (27.4 %) patients completed the trial (up to 14 years of treatment with BRV) and 619 (72.6 %) patients discontinued the trial (Fig. S1). Reasons for discontinuation were lack of efficacy (354 [41.5 %] patients), adverse event (100 [11.7 %]), patient choice (98 [11.5 %]), lost to follow-up (17 [2.0 %]), and other (50 [5.9 %]). Discontinuations due to lack of efficacy and due to adverse events were similar in the focal and generalized onset seizure subgroups (lack of efficacy: 312 [42.8 %], 12 [40.0 %]; adverse events: 79 [10.8 %]; 3 [10.0 %]). In the ULD subgroup, 30 (31.9 %) patients discontinued due to lack of efficacy, and 18 (19.1 %) discontinued due to adverse events.

The total duration of BRV exposure was 3477.5 patient-years. The numbers of patients completing ≥12, ≥24, ≥36, ≥60, and ≥96 months of treatment were 588 (68.9 %), 472 (55.3 %), 403 (47.2 %), 322 (37.7 %), and 223 (26.1 %), respectively (Table S2). Eight patients remained on BRV for ≥156 months (13 years); one patient remained in the trial for up to 165 months. The proportion of patients completing ≥96 months of treatment was higher in the ULD subgroup (37 [39.4 %]), than in patients with focal (184 [25.2 %]) or generalized onset seizures (2 [6.7 %]). In the overall population, the most common modal doses of BRV were 150 mg/day (415 [48.7 %] patients) and 100 mg/day (262 [30.7 %]) (Table S3). Nine patients (seven with focal seizures, one with generalized onset seizures, and one with ULD) received a total daily dose of BRV >200 mg/day; these doses ranged from 225 to 300 mg/day, and were taken for 1 day only with the exception of the patient with ULD. The most common modal dose of BRV was 150 mg/day (370/729 [50.8 %]) for patients with focal seizures, 150 mg/day (13/30 [43.3 %]) for patients with generalized onset seizures, and 100 mg/day (44/94 [46.8 %]) for patients with ULD; 34 (4.7 %) patients with focal seizures and 9 (9.6 %) patients with ULD had a modal dose of 200 mg/day.

Patients had a mean age of 37.5 years and 51.0 % were male

Table 2
Baseline[a] epilepsy characteristics and concomitant antiseizure medications (ES).

	Focal seizures (N = 729)	Generalized onset seizures (N = 30)
Epilepsy duration, mean (SD), years[b]	23.1 (13.0)	18.1 (9.6)
Age at time of first seizure, mean (SD), years	15.0 (11.3)	11.8 (9.2)
Seizure types experienced at any time before entry into previous trial, n (%)[c]		
Any partial-onset seizures (focal seizures)	729 (100)	0
Simple partial (focal aware)	292 (40.1)	0
Complex partial (focal impaired awareness)	648 (88.9)	0
Partial evolving to secondary generalized (focal to bilateral tonic-clonic)	490 (67.2)	0
Any generalized seizures	30 (4.1)	30 (100)
Absence	7 (1.0)	16 (53.3)
Myoclonic	3 (0.4)	4 (13.3)
Clonic	0	4 (13.3)
Tonic	4 (0.5)	6 (20.0)
Tonic-clonic	22 (3.0)	24 (80.0)
Atonic	3 (0.4)	3 (10.0)
Number of previous ASMs, n (%)[d]		
0–1	191 (26.2)	10 (33.3)
2–4	386 (52.9)	16 (53.3)
≥5	152 (20.9)	4 (13.3)
Concomitant ASMs taken by ≥10 % of patients in either subgroup, n (%)[e]		
Carbamazepine	322 (44.2)	9 (30.0)
Lamotrigine	227 (31.1)	15 (50.0)
Levetiracetam	199 (27.3)	7 (23.3)
Topiramate	170 (23.3)	8 (26.7)
Oxcarbazepine	159 (21.8)	2 (6.7)
Valproate sodium	136 (18.7)	6 (20.0)
Clobazam	90 (12.3)	3 (10.0)
Clonazepam	66 (9.1)	6 (20.0)
Valproic acid	72 (9.9)	5 (16.7)
Zonisamide	66 (9.1)	4 (13.3)
Lacosamide	71 (9.7)	3 (10.0)

ASM, antiseizure medication; ES, Efficacy Set; SD, standard deviation.

[a] Baseline refers to data collected at the time of entry into the previous trials or from the Baseline period of the previous trials.

[b] Relative to date of first seizure.

[c] Patients could have more than one response in a classification level and/or category; seizure types are listed per the International League Against Epilepsy (ILAE), 1981 classification (1981), with the newer terminology (Fisher et al., 2017) provided in parentheses.

[d] Taken within 5 years prior to, and discontinued before, entry into the previous trial.

[e] Taken during administration of brivaracetam in the current trial, regardless of start and stop dates.

Table 1
Patient baseline demographics (SS).

	All patients (N = 853)	Focal seizures (N = 729)	Generalized onset seizures (N = 30)	ULD (N = 94)
Age, mean (SD), years	37.5 (11.8)	37.9 (12.0)	29.7 (9.0)	37.1 (10.4)
≤18 years, n (%)	14 (1.6)	12 (1.6)	0	2 (2.1)
19 to <65 years, n (%)	827 (97.0)	705 (96.7)	30 (100)	92 (97.9)
≥65 years, n (%)	12 (1.4)	12 (1.6)	0	0
Male, n (%)	435 (51.0)	373 (51.2)	15 (50.0)	47 (50.0)

SD, standard deviation; SS, Safety Set; ULD, Unverricht–Lundborg disease.

Table 3
Treatment-emergent adverse events (SS).

	All patients ($N = 853$)	Focal seizures ($N = 729$)	Generalized onset seizures ($N = 30$)	ULD ($N = 94$)
Any TEAEs, *n* (%)	720 (84.4)	610 (83.7)	23 (76.7)	87 (92.6)
Drug-related TEAEs, *n* (%)[a]	451 (52.9)	375 (51.4)	16 (53.3)	60 (63.8)
Serious TEAEs, *n* (%)	248 (29.1)	199 (27.3)	7 (23.3)	42 (44.7)
Drug-related serious TEAEs, *n* (%)[a]	57 (6.7)	41 (5.6)	2 (6.7)	14 (14.9)
Severe TEAEs, *n* (%)	216 (25.3)	170 (23.3)	6 (20.0)	40 (42.6)
Discontinuations due to TEAEs, *n* (%)	95 (11.1)	76 (10.4)	3 (10.0)	16 (17.0)
Deaths, *n* (%)	19 (2.2)	11 (1.5)	0	8 (8.5)
Most common TEAEs (≥10 % of patients in any group), n (%)[b]				
Headache	188 (22.0)	158 (21.7)	6 (20.0)	24 (25.5)
Nasopharyngitis	157 (18.4)	140 (19.2)	3 (10.0)	14 (14.9)
Convulsion[c]	137 (16.1)	117 (16.0)	10 (33.3)	10 (10.6)
Dizziness	123 (14.4)	107 (14.7)	5 (16.7)	11 (11.7)
Fatigue	86 (10.1)	72 (9.9)	3 (10.0)	11 (11.7)
Diarrhea	79 (9.3)	60 (8.2)	4 (13.3)	15 (16.0)
Back pain	79 (9.3)	62 (8.5)	3 (10.0)	14 (14.9)
Urinary tract infection	78 (9.1)	61 (8.4)	1 (3.3)	16 (17.0)
Somnolence	75 (8.8)	56 (7.7)	3 (10.0)	16 (17.0)
Depression	67 (7.9)	52 (7.1)	1 (3.3)	14 (14.9)
Influenza	66 (7.7)	51 (7.0)	2 (6.7)	13 (13.8)
Nausea	56 (6.6)	49 (6.7)	3 (10.0)	4 (4.3)
Arthralgia	54 (6.3)	40 (5.5)	2 (6.7)	12 (12.8)
Upper respiratory tract infection	52 (6.1)	40 (5.5)	1 (3.3)	11 (11.7)
Contusion	49 (5.7)	38 (5.2)	4 (13.3)	7 (7.4)
Fall	49 (5.7)	37 (5.1)	1 (3.3)	11 (11.7)
Upper abdominal pain	43 (5.0)	29 (4.0)	5 (16.7)	9 (9.6)

SS, Safety Set; TEAE, treatment-emergent adverse event; ULD, Unverricht–Lundborg disease.
[a] The relationship was assessed by the investigator.
[b] Medical Dictionary for Regulatory Activities Version 15.0 Preferred Term.
[c] Signs or symptoms of the condition/disease for which brivaracetam was being studied should have been recorded as adverse events only if their nature changed considerably, or their frequency or intensity increased in a clinically significant manner as compared with the clinical profile known to the investigator from the patient's history or the Baseline period.

(Table 1). No meaningful differences in age or gender were observed between the focal seizure and ULD subgroups. Patients with generalized onset seizures were younger on average. In the overall population, most patients (765 [89.7 %]) reported at least one prior or ongoing medical condition at Baseline of the previous double-blind trials, most commonly (≥5 % of all patients) head injury (83 [9.7 %]), depression (81 [9.5 %]), headache (74 [8.7 %]), hypertension (65 [7.6 %]), vagal nerve stimulator implantation (62 [7.3 %]), and appendicectomy (59 [6.9 %]).

Data for Baseline epilepsy characteristics, concomitant ASMs and classification of epileptic syndrome are available for patients with focal seizures and generalized onset seizures only (Table 2; Table S4). Patients with focal seizures had a mean epilepsy duration of 23.1 years, and 20.9 % had taken five or more ASMs in the 5 years prior to entry in the previous trial. Patients with generalized onset seizures had a mean epilepsy duration of 18.1 years, and 13.3 % had taken five or more previous ASMs.

3.2. Long-term safety and tolerability

A total of 720 (84.4 %) patients in the SS reported at least one TEAE (Table 3). The incidence of TEAEs was higher in Months 1–3 (473/853 [55.5 %] patients) than in Months 4–6 (282/775 [36.4 %] patients), as well as subsequent 3-month time intervals (range: 0–32.5 %). Four hundred and fifty-one (52.9 %) patients had TEAEs that were considered drug-related by the investigator, most commonly (≥5 % of patients) dizziness (60 [7.0 %]), fatigue (53 [6.2 %]), somnolence (52 [6.1 %]), and convulsion (50 [5.9 %]). Two hundred and forty-eight (29.1 %) patients had a serious TEAE and 95 (11.1 %) had a TEAE leading to permanent discontinuation of BRV. Serious TEAEs reported by ≥1 % of patients were convulsion (36 [4.2 %]), epilepsy (11 [1.3 %]), head injury (10 [1.2 %]), status epilepticus (10 [1.2 %]), myoclonus (nine [1.1 %]), and pneumonia (nine [1.1 %]). TEAEs leading to BRV discontinuation in at least four patients were convulsion (nine [1.1 %]), pregnancy (nine [1.1 %]), irritability (five [0.6 %]), depression (five [0.6 %]), fatigue (four [0.5 %]), and suicidal ideation (four [0.5 %]).

In the focal and generalized onset seizure subgroups, the incidences of TEAEs, drug-related TEAEs, and serious TEAEs were comparable to those observed in the overall population (Table 3). In the ULD subgroup, 87 (92.6 %) patients reported TEAEs and 60 (63.8 %) patients reported TEAEs that were considered to be drug-related by the investigator. The most common TEAEs (≥15 % of patients) were headache, urinary tract infection, somnolence, and diarrhea (Table 3). Forty-two (44.7 %) patients had a serious TEAE, and 16 (17.0 %) had a TEAE leading to permanent discontinuation of BRV.

In the overall population, 79 (9.3 %) patients reported TEAEs that were potentially associated with behavioral disorders. The incidence of behavioral TEAEs was highest during Months 1–3 (31 [3.6 %] patients) and decreased thereafter across subsequent 3-month time intervals (range: 0–1.4 %). The most common behavioral TEAEs (at least four patients) were irritability (35 [4.1 %]), aggression (26 [3.0 %]), abnormal behavior (nine [1.1 %]), agitation (eight [0.9 %]), and anger (five [0.6 %]). TEAEs potentially associated with suicidality or suicidal ideation were reported by 149 patients (17.5 %), most commonly (≥2 % of patients) depression (67 [7.9 %]), laceration (31 [3.6 %]), depressed mood (28 [3.3 %]), and suicidal ideation (23 [2.7 %]). Three (0.4 %) patients with focal seizures reported suicide attempt, and two (0.2 %) patients with ULD reported suicidal behavior; none of these events were considered drug-related. No completed suicides were reported.

During this long-term trial of up to 14 years in duration, 19 (2.2 %) patients died; 11 had focal seizures and eight had ULD (Table 3 and Table S5). One death was recorded as drug-related by the investigator; this occurred in a patient with focal seizures and was described as 'death without primary diagnosis'. Two deaths were clearly associated with epilepsy. One patient died from ULD (severe Baltic myoclonic epilepsy) while experiencing moderate depression (not drug-related) and moderate aggression (drug-related). An additional patient with focal seizures had a fatal event of generalized tonic-clonic seizure (grand mal convulsion) and status epilepticus.

No clinically relevant findings were observed for any mean changes from Baseline in hematology, blood chemistry, urinalysis parameters, vital signs, body weight, or electrocardiograms. Among patients with focal or generalized onset seizures and available HADS data ($n = 523$), mean scores indicated normal levels of anxiety and depression which generally remained stable from Baseline of the previous trial to the last value in Year 2 (Table S6).

3.3. Efficacy variables: patients with focal seizures

At Baseline of the previous double-blind trials, patients with focal seizures (ES: $N = 729$) had a median (Q1, Q3) of 8.4 (5.0, 16.1) focal seizures per 28 days. Median (Q1, Q3) focal seizure frequency during the Evaluation Period was 4.9 (2.1, 10.8) seizures per 28 days. Median percent reduction in focal seizure frequency from double-blind Baseline for the entire Evaluation Period was 43.1 % (Fig. 1). In patients completing 12 ($n = 500$), 36 ($n = 338$), and 60 ($n = 272$) months of treatment, median percent reduction in focal seizure frequency was 52.6 %, 59.5 %, and 62.1 %, respectively (Fig. 1A). Within each completer cohort, median percent reductions in focal seizure frequency were maintained over time (Fig. 1B).

For patients with focal seizures, the overall 50 % responder rate for focal seizure frequency was 43.6 % (Fig. 2). The 50 % responder rates ranged from 46.7 % in the 6-month completer cohort to 63.0 % in the 96-month completer cohort. Overall, 22.2 % of patients remained seizure-free (all seizure types) on BRV treatment for at least 6 months and 15.8 % remained seizure-free for at least 12 months (Fig. 3). The percentage of patients who remained seizure-free for at least 6 months ranged from 4.0 % in the 6-month cohort to 40.8 % in the 96-month cohort, and 12-month seizure-freedom ranged from 4.2 % in the 12-month cohort to 29.3 % in the 96-month cohort.

In the post hoc analyses of patients with focal seizures, patients with previous LEV exposure ($N = 196$) had a higher number of ASMs taken and discontinued within the last 5 years before entry into N01125 (median 4.0) compared with patients who were LEV-naïve ($N = 334$; median 2.0), and higher proportion of patients with five or more previous ASMs (41.3 % vs 7.8 %) (SS; Table S7). The median percent reduction from Baseline in focal seizure frequency, the 50 % responder rate, and the rates of continuous seizure-freedom for ≥6 and ≥12 months were numerically higher in patients who were LEV-naïve compared with patients previously exposed to LEV (ES; Table S8).

3.4. Efficacy variables: patients with generalized onset seizures

Patients with generalized onset seizures (ES: $N = 30$) had a median (Q1, Q3) of 5.7 (3.9, 12.8) generalized onset seizure days at Baseline of the double-blind trials. The median percent reduction in generalized onset seizure days for the entire Evaluation Period was 43.2 % ($n = 29$).

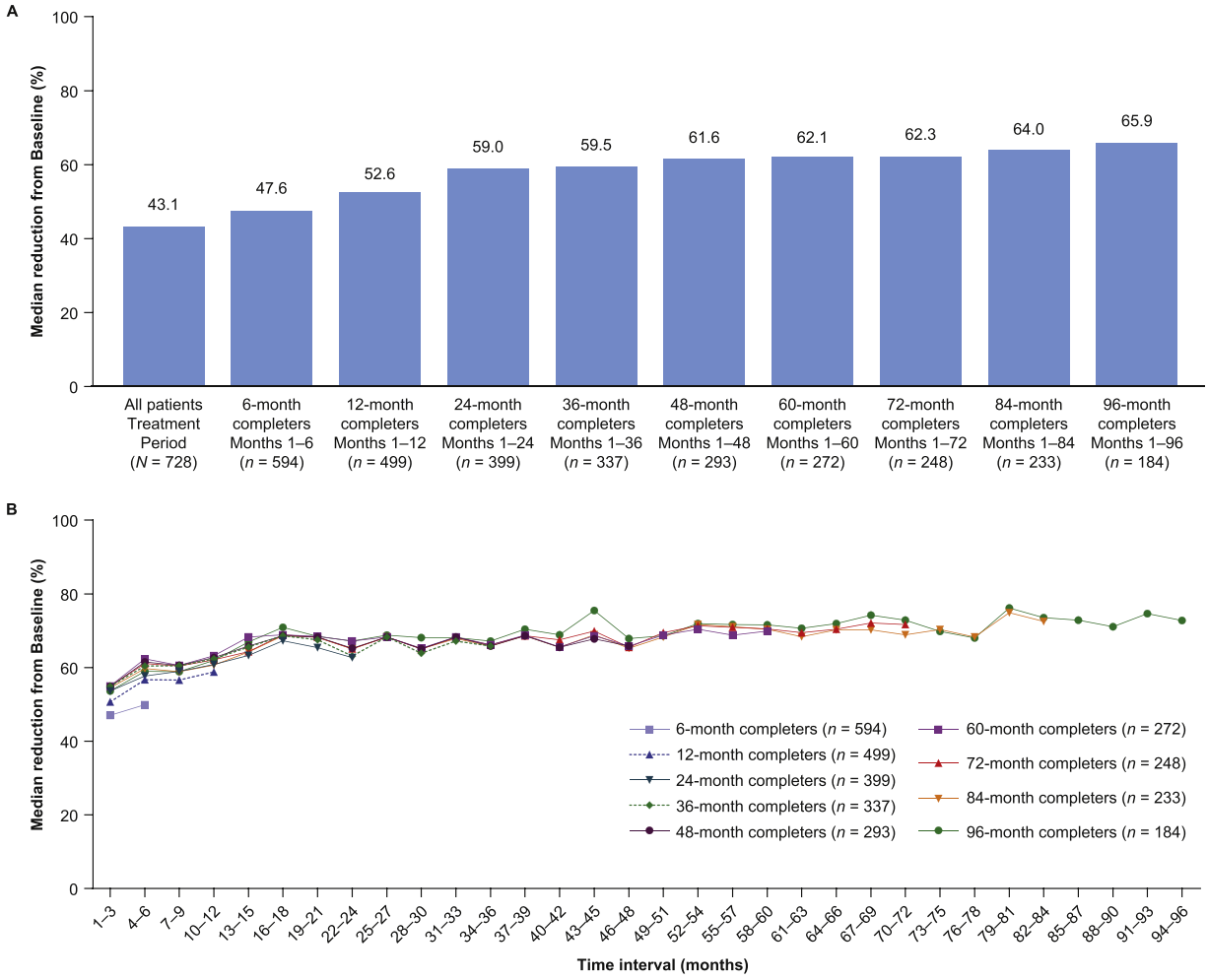

Fig. 1. Median percent reduction from double-blind Baseline of the previous trial in focal seizure frequency/28 days by completer cohorts (focal seizure ES). (A) Overall, and (B) by 3-month time intervals.
BRV, brivaracetam; ES, Efficacy Set.
Completer cohorts included patients with at least the specified duration of BRV exposure.

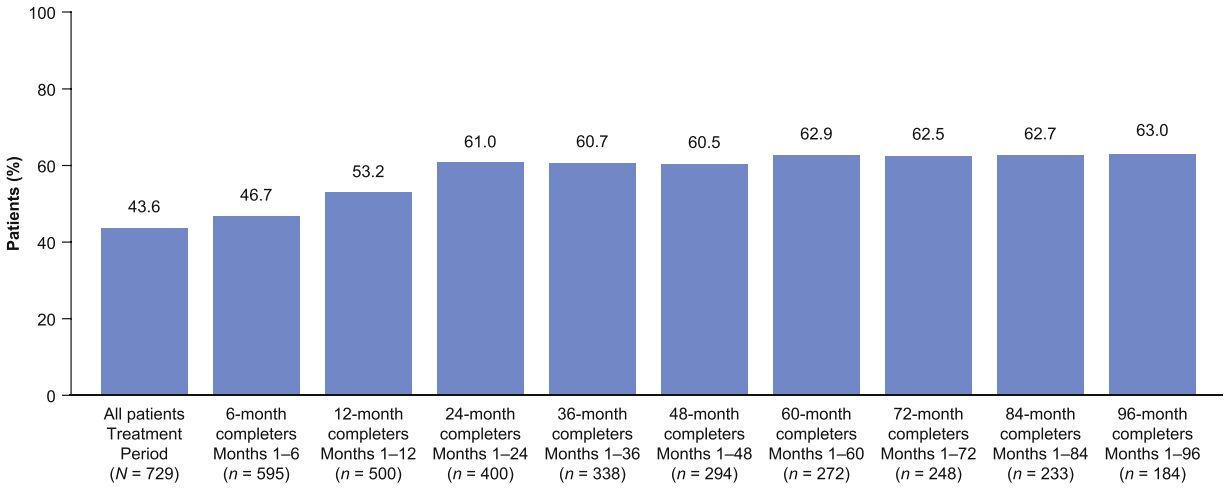

Fig. 2. 50 % responder rate for focal seizure frequency (focal seizure ES).
BRV, brivaracetam; ES, Efficacy Set.
Completer cohorts included patients with at least the specified duration of BRV exposure.

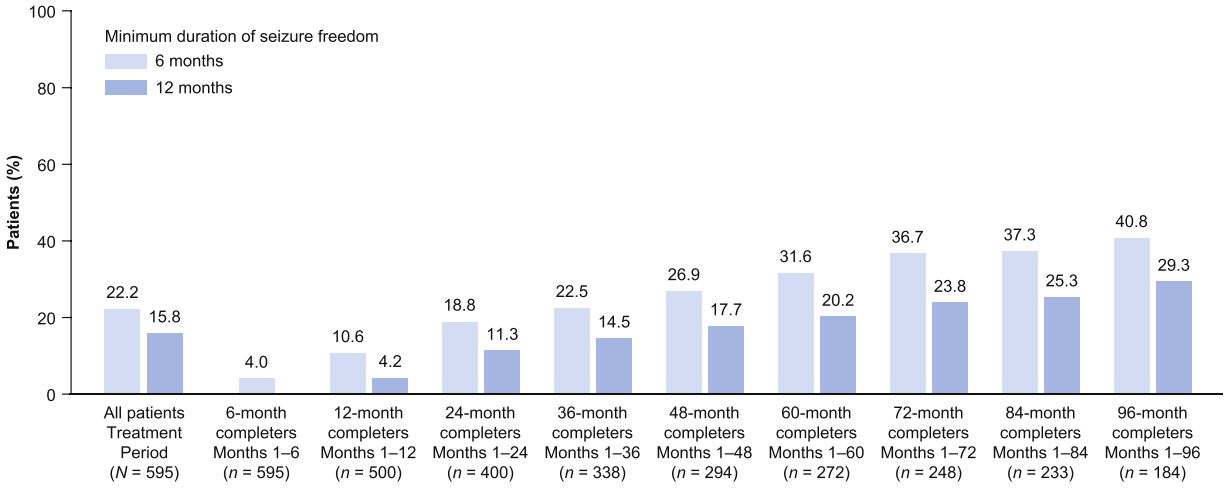

Fig. 3. Continuous seizure-freedom (all seizure types) for ≥6 and ≥12 months (focal seizure ES). Patients were considered to be seizure-free if they reported no seizures during the specified time interval, and had a complete seizure diary for ≥90 % of days within the time interval. Patients with a duration of BRV treatment that was less than the specified duration of seizure-freedom were considered failures for seizure-freedom.
BRV, brivaracetam; ES, Efficacy Set.
Completer cohorts included patients with at least the specified duration of BRV exposure.

The 50 % responder rate for generalized onset seizure days during the Evaluation Period was 43.3 %. Overall, 29.6 % of patients with generalized onset seizures remained seizure-free (all seizure types) on BRV treatment for at least 6 months, and 22.2 % remained seizure-free for at least 12 months ($n = 27$).

3.5. *Quality of life*

In patients with focal seizures, mean QOLIE-31-P scores (Table S9) and EQ-5D scores (Table S10) generally remained stable or improved from Baseline of the previous trial to the last value in Year 2.

4. Discussion

Long-term treatment with adjunctive BRV was generally well tolerated at individualized doses up to 200 mg/day in patients with focal seizures, generalized onset seizures, and ULD. Patients received BRV for up to 14 years, with 55.3 % treated for more than 2 years and 26.1 % for more than 8 years. The timing of locally approved commercial availability of BRV affected the overall duration of exposure, as patients were converted to commercial BRV or transitioned to a managed access program as soon as BRV was available.

The discontinuation rate of 72.6 %, with 41.5 % of patients discontinuing because of a lack of efficacy, may be reflective of the long trial duration and a difficult-to-treat patient population. Patients enrolled in the initial double-blind trials had uncontrolled focal or generalized seizures despite treatment with one to three ASMs, or ULD with moderate to severe myoclonus (action myoclonus score ≥30/160) (Arnold et al., 2020; Kälviäinen et al., 2016; Kwan et al., 2014; Ryvlin et al., 2014; Van Paesschen et al., 2013). A high baseline seizure frequency was observed in patients in the focal seizure (median of 8.4 focal seizures per 28 days) and generalized onset seizure subgroups (median of 5.7 generalized onset seizure days per 28 days). Furthermore, approximately half of the patients with focal and generalized onset seizures continuing to this long-term follow-up trial had taken between two and four previous ASMs within the 5 years prior to entry to the double-blind trial, and 20.9 % of patients with focal seizures and 13.3 % of patients with generalized onset seizures had taken five or more

previous ASMs. These data indicate that the enrolled patients represent a drug-resistant patient population.

The safety and tolerability profile of BRV demonstrated in this OLE trial was consistent with that observed in pooled Phase IIb/III and long-term follow-up BRV trials, where 84.5 % of patients experienced at least one TEAE (Toledo et al., 2016). Overall, TEAEs were reported by 84.4 % of all patients during long-term BRV treatment in the current trial. The incidence of TEAEs was higher during Months 1–3 compared with later timepoints, with similar results observed in another OLE trial of BRV (O'Brien et al., 2020). This was not unexpected because patients who received placebo in the double-blind trials received BRV for the first time in this OLE, and some patients were up-titrated, receiving a higher dose of BRV when they transitioned to this trial. Furthermore, patients who were less able to tolerate BRV may have discontinued from the trial during the first 3 months. The most common TEAEs in the current trial were headache, nasopharyngitis, dizziness, and fatigue, in line with the safety profile of BRV observed in the pooled analysis of BRV trials (Toledo et al., 2016). The incidence of permanent discontinuation of BRV treatment because of TEAEs (11.1 %) was also comparable with pooled data of Phase IIb/III and long-term (≥8.0 years) follow-up trials (12.1 %) (Toledo et al., 2016).

Behavioral TEAEs such as aggression and anger are associated with ASM use, and appear to be most common with LEV and zonisamide (Chen et al., 2017). BRV and LEV both act through binding to SV2A in the brain; however, BRV has a more selective SV2A receptor interaction (Gillard et al., 2011). Among patients treated with BRV for up to 14 years in this OLE trial, the overall incidence of TEAEs potentially associated with behavioral disorders was low (9.3 %). The incidences of the most common potentially behavioral TEAEs, irritability (4.1 %), and aggression (3.0 %), were comparable with those reported in the pooled long-term BRV trials (5.2 %; 1.7 %) (Toledo et al., 2016), and an in-depth pooled analysis of the safety and tolerability of adjunctive BRV (2.7 %; 0.7 %) (Brandt et al., 2020).

Patients with ULD and moderate to severe myoclonus were enrolled from two double-blind trials (N01187 and N01236). Analyses of the double-blind trial data showed the effect of BRV on action myoclonus was not significantly different from placebo. However, BRV was generally well tolerated and the majority of patients chose to continue to the OLE (Kälviäinen et al., 2016). No efficacy assessments were performed for patients with ULD in the current trial; however, this OLE trial is to our knowledge the longest and largest follow-up trial of ASM treatment in patients with this rare epilepsy syndrome. In this trial, patients with ULD treated with BRV had a good safety and tolerability profile, which is consistent with results from the double-blind placebo-controlled ULD trials where BRV was well tolerated up to 150 mg/day (Kälviäinen et al., 2016). While the highest permitted dose of BRV in the previous trial for patients with ULD was 150 mg/day, 9.6 % of patients with ULD had a modal dose of 200 mg/day in this OLE. In comparison to the patients with focal or generalized seizures, patients with ULD had a higher incidence of TEAEs (92.6 % vs 83.7 %/76.7 %), serious (44.7 % vs 27.3 %/23.3 %) and severe TEAEs (42.6 % vs 23.3 %/20.0 %), a higher rate of discontinuations due to TEAEs (17.0 % vs 10.4 %/10.0 %), and a higher incidence of deaths (8.5 % vs 1.5 %/0.0 %). These differences could be attributed to the more severely impaired health status of patients with ULD. Retention on BRV was relatively high, with 39.4 % of patients with ULD completing at least 8 years (96 months) of treatment. This suggests that patients who were able to tolerate BRV benefited from long-term treatment.

Given the open-label trial design and lack of a comparator group, all efficacy analyses are descriptive in nature. In general, patients with focal seizures who remained in the trial and on BRV treatment showed improvements in focal seizure frequency. Efficacy assessments in long-term extension trials should be interpreted with caution, as patients who respond well in the previous double-blind trial are more likely to continue to the OLE and to remain on treatment over several years. In order to address partly the potential selection bias that patients with a poorer response are more likely to discontinue over time, efficacy analyses were also performed for completer cohorts. Analyses by 3-month intervals for cohorts of patients completing at least 6 months of treatment indicated that reductions in focal seizure frequency were generally sustained over time. Interpretation of the data for patients with generalized onset seizures is limited by the small sample size; however, the results suggest that BRV may be efficacious in this patient population.

A systematic literature review of data from randomized controlled trials suggested a greater efficacy of BRV in patients who were LEV-naïve compared to those with previous LEV exposure (Lattanzi et al., 2016). In this trial, long-term adjunctive BRV treatment was effective in patients with previous exposure to LEV and those naïve to LEV. The efficacy of BRV was numerically lower in patients previously exposed to LEV compared with that observed in the overall trial population of patients with focal seizures. This may be because a higher proportion of patients with previous LEV exposure had a larger number of previous ASMs in the 5 years prior to double-blind trial entry, with 41.3 % having taken five or more previous ASMs, and may represent a more drug-resistant patient population. These data are consistent with reports indicating that previous exposure to commonly used ASMs (LEV, carbamazepine, topiramate, and lamotrigine) was associated with a reduced response to BRV, irrespective of the mechanism of action of the previous ASM (Asadi-Pooya et al., 2017), and patients with fewer previous (Ben-Menachem et al., 2016) or lifetime (Klein et al., 2020) ASMs had a generally higher response to BRV. These results are not unexpected because studies have shown that clinical response to a newly administered ASM is highly dependent on the past ASM treatment history (Luciano and Shorvon, 2007), and increasing number of previous ASMs is associated with a lower treatment response (Schiller and Najjar, 2008).

Overall, data from this OLE trial support the long-term safety of adjunctive BRV at individualized doses of up to 200 mg/day in patients with focal seizures, generalized onset seizures, and ULD. Improvements in focal seizure frequency with BRV were maintained over time, and no new safety or tolerability signals were observed.

Data statement

Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents which may include: analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password protected portal.

Declaration of Competing Interest

Elinor Ben-Menachem has been a paid consultant for GW Pharmaceuticals and UCB Pharma. Michel Baulac has served as a paid consultant for Eisai, GlaxoSmithKline, Sage Therapeutics, GW Pharmaceuticals, and UCB Pharma. Seung Bong Hong has no conflicts of interest to declare. Jody M Cleveland and Anne-Liv Schulz are employees of UCB Pharma. Christoph Reichel and Gilbert Wagener are contracted by UCB Pharma. Christian Brandt has received personal compensation from Arvelle, Desitin, Eisai, GW Pharmaceuticals, Idorsia, and UCB Pharma for serving on an advisory board or serving as a speaker, or support for congress travel.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi: https://doi.org/10.1016/j.eplepsyres.2020.106526.

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