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Long-term safety, efficacy, and quality of life during adjunctive brivaracetam treatment in patients with uncontrolled epilepsy: An open-label follow-up trial

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ABSTRACT

Objectives: The primary objective of this long-term follow-up (LTFU) trial was to evaluate the long-term safety and tolerability of brivaracetam (BRV). The secondary objective was to evaluate the maintenance of efficacy of BRV (including quality of life) over time.
Methods: This open-label, multicenter, flexible-dose trial (N01379 [NCT01339559]) was conducted in adults (≥16 years) with focal or generalized-onset seizures, who had participated in a placebo (PBO)-controlled trial of adjunctive BRV (N01258: NCT01405508 or N01358: NCT01261325).
Results: Seven hundred and sixty-six patients received BRV in this LTFU trial (753 had focal seizures and 13 had generalized-onset seizures). Kaplan–Meier-estimated retention was 71.9% at 12 months, and 53.7% at 36 months. Treatment-emergent adverse events (TEAEs) were reported by 643 (83.9%) patients, most commonly headache (104 [13.6%] patients) and dizziness (100 [13.1%] patients). Two hundred and fifty-seven (33.6%) patients had drug-related TEAEs, most commonly somnolence (49 [6.4%] patients) and dizziness (41 [5.4%] patients). Permanent discontinuation of BRV due to TEAEs occurred in 91 (11.9%) patients. Patients with focal seizures had a median percentage reduction in focal seizure frequency of 52.0% and 51.7% were 50% responders (sustained over time); 26.0% were seizurefree for 6 months, and 17.9% were seizurefree for 12 months. 42.4% of patients at 12 months and 46.8% at 24 months had clinically meaningful improvements in Patient Weighted Quality of Life in Epilepsy Questionnaire 31 total score.
Conclusions: In this select group of patients who entered the LTFU trial, BRV was generally safe and well tolerated. Results indicate the long-term efficacy of BRV in patients with focal seizures.

1. Introduction

Epilepsy usually requires long-term treatment with antiepileptic drugs (AEDs) [1]. Consequently, it is important to establish the long-term safety, tolerability, and efficacy of the AED. Brivaracetam (BRV) is an AED that displays a high and selective affinity for the synaptic vesicle 2A protein [2,3]. Brivaracetam may allow seizure control from the first day of treatment [4,5], and has a low potential for clinically relevant pharmacokinetic drug–drug interactions with other AEDs [6,7]. Brivaracetam is indicated in patients 4 years of age and older with focal (partial-onset) seizures with or without

Abbreviations: AE, adverse event; AED, antiepileptic drug; BRV, brivaracetam; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ES, Efficacy Set; HADS, Hospital Anxiety and Depression Scale; LTFU, long-term follow-up; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; QOLIE-31-P, Patient Weighted Quality of Life in Epilepsy Questionnaire 31; SD, standard deviation; SS, Safety Set; TEAE, treatment-emergent adverse event.

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secondary generalization as adjunctive treatment in the European Union [8] and as monotherapy and adjunctive treatment in the United States (oral formulations only; BRV injection is currently only indicated for patients ≥ 16 years of age) [9]. Brivaracetam is also approved in multiple countries globally, including several across North and South America and the Asia Pacific region.

An open-label, long-term follow-up (LTFU) trial (N01379) of adjunctive BRV has been conducted in adults with mainly focal seizures. This trial (N01379) enrolled patients who completed one of two double-blind placebo (PBO)-controlled trials of adjunctive BRV (N01258 or N01358) (Table S1). N01258 evaluated adjunctive intravenous BRV 200 mg/day administered twice daily as 2-min bolus or 15-min infusion (as BRV initiation or conversion from oral BRV) in adults with focal or generalized-onset seizures [10]. N01358 evaluated oral BRV 100 or 200 mg/day in adults with focal seizures [11]. The primary objective of this LTFU trial was to evaluate the long-term safety and tolerability of BRV at individualized doses up to a maximum of 200 mg/day in patients with epilepsy. The secondary objective was to evaluate the maintenance of efficacy of BRV (including quality of life) over time.

2. Methods

2.1. Trial design

This open-label, LTFU, multicenter, flexible-dose, single-arm trial (N01379 [NCT01339559]; BRITE) was conducted in adult patients (≥16 years) with focal or generalized-onset seizures. Patients were eligible to enroll in N01379 if they had previously participated in a PBO-controlled trial of adjunctive BRV (N01258: NCT01405508 or N01358: NCT01261325) (Table S1). In both of the previous trials, patients had uncontrolled epilepsy despite treatment with one to two concomitant AEDs.

Patients who completed the Evaluation Period of N01258 or the Treatment Period of N01358 and were expected to benefit from long-term administration of BRV by the investigator were included. Exclusion criteria included severe medical, neurological, and psychiatric disorders or laboratory values that may have had an impact on the safety of the patient, and poor adherence to the visit schedule or medication intake in the previous trial. In addition, patients who had a lifetime history of suicide attempt, or had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the Columbia-Suicide Severity Rating Scale (C-SSRS) at entry into N01379 were excluded. Women who were pregnant, lactating, or of childbearing potential and not using approved methods of contraception (unless sexually abstinent) were also excluded.

All patients provided written informed consent before enrollment. Patients who enrolled in the LTFU trial immediately entered the Evaluation Period. Patients started LTFU on an oral BRV dose of 200 mg/day (patients from N01258) or 150 mg/day (N01358). Patients were maintained at these doses for at least 2 weeks unless unable to tolerate treatment. The BRV dose could subsequently have been adjusted based on each patient's seizure control and tolerability, without exceeding 200 mg/day. Patients had a flexible concomitant AED regimen. For each patient, the trial lasted until regulatory approval of adjunctive BRV treatment for focal seizures had been granted; until the sponsor decided to close the trial; until patients transitioned to another BRV trial or access program; or until the patient transitioned to commercial BRV. Patients who discontinued BRV entered a Down-Titration Period (up to 4 weeks) followed by a Post-Treatment Period (2–4 weeks) during which the patient did not receive BRV.

Visits were scheduled to occur once per month in the first 3 months and once every 3 months thereafter. C-SSRS assessments were carried out at each visit, with any findings reported as adverse events (AEs). The trial protocol, amendments, and patient informed consent forms were reviewed by a national or regional independent ethics committee or institutional review board. The trial was conducted in accordance with the International Council for Harmonization-Good Clinical Practice, the Declaration of Helsinki, and local laws.

2.2. Outcome measures

Primary safety variables included occurrence of a treatment-emergent adverse event (TEAE), withdrawal due to TEAE, and occurrence of serious TEAEs. Signs or symptoms of epilepsy (e.g., convulsion) were recorded as TEAEs only if their nature changed considerably or their frequency or intensity increased in a clinically significant manner. Individual psychiatric TEAEs were identified based on the Medical Dictionary for Regulatory Activities (MedDRA v15.0) "Psychiatric disorders" system organ class. TEAEs potentially associated with behavioral disorders, and TEAEs potentially associated with suicidality or suicidal ideation were identified using a list of preferred terms, which was previously defined by a comprehensive medical review of the MedDRA v15.0 preferred terms [12]. Other safety variables included laboratory tests (hematology, blood chemistry, endocrinology, urinalysis), vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), body weight, electrocardiogram (ECG), and physical and neurological examinations. Change in Hospital Anxiety and Depression Scale (HADS) scores [13] from Baseline of the previous trial was assessed during the first 2 years of the Evaluation Period. Depression and anxiety were scored separately from 0 to 21. A post hoc analysis of depression and anxiety score categories (normal: 0–7; borderline abnormal: 8–10; abnormal moderate: 11–14; and abnormal severe: 15–21) at Baseline, 12, and 24 months was also performed.

Efficacy variables for patients with focal seizures included percentage reduction in focal seizure frequency/28 days from Baseline of the previous trial to the Evaluation Period, responder rate for the Evaluation Period (defined as ≥50% reduction in focal seizure frequency from Baseline of the previous trial), percentage of patients continuously seizure-free (all seizure types) for any 6- or 12-month interval during the Evaluation Period, and change in Patient Weighted Quality of Life in Epilepsy Questionnaire 31 (QOLIE-31-P) scores [14] from Baseline of the previous trial during the first 2 years of the Evaluation Period (scores range from 0 to 100 with higher scores corresponding to better functioning/health status). A post hoc analysis of the proportion of patients with clinically meaningful improvements in QOLIE-31-P scores was also performed, based on previously defined minimally important change thresholds [15]. Efficacy variables for patients with generalized-onset seizures included percentage of patients continuously seizure free (all seizure types) for any 6- or 12-month interval during the Evaluation Period. Other efficacy variables were not assessed for patients with generalized-onset seizures, because these patients did not have reliable Baseline seizure frequency data.

2.3. Statistical methods

Results were summarized using descriptive statistics; no hypothesis testing was done. Baseline for all trial outcomes was the previous trial Baseline (before BRV/PBO treatment). Safety analyses were conducted in the Overall Safety Set (SS; all patients who took at least one dose of trial medication in the LTFU trial), Focal Seizures SS (patients in the Overall SS with focal seizures whether or not secondarily generalized, from both the N01258 and N01358 trials), and Generalized Seizures SS (patients in the Overall SS with generalized-onset seizures [from the N01258 trial]

as assigned by the investigator based on diagnosis or medical history). Efficacy analyses were conducted in the Focal Seizures Efficacy Set (ES) and Generalized Seizures ES (patients in the Focal Seizures/Generalized Seizures SS who had at least one day of their seizure diary completed during the LTFU Evaluation Period).

For seizure assessments, patients were classified into completer cohorts which reflect their minimum exposure period during the trial. For example, patients were included in the 12-month completer cohort if they had completed at least 12 months of BRV treatment (a month was defined as 30 days). The date and number of seizures were recorded by patients using a daily record card. N01258 was a safety trial and patients were not required to meet seizure frequency requirements; there was no reliable Baseline seizure frequency as the Baseline Period was just 7 days. Therefore, patients from N01258 were excluded from assessments of percentage reduction in focal seizure frequency/28 days and responder rates. However, patients from N01258 were included in the assessment of seizure freedom because this variable was independent from Baseline. Patients were considered to have 6- or 12-month seizure freedom if they reported no seizures during BRV treatment for 6 or 12 months at any time during the cohort interval, and the seizure diary was completed for at least 90% of days within the seizure-free interval. Patients whose duration of BRV treatment was less than the duration of seizure freedom were failures for seizure freedom.

The proportion of patients completing specified durations of treatment from the first BRV dose in the LTFU trial was assessed by Kaplan–Meier methods. Patients who permanently discontinued BRV were analyzed as events on the last day of treatment with BRV. Patients who completed the trial were censored on the last day of treatment with BRV. In addition, a post hoc Kaplan–Meier analysis was carried out in which patients who did not discontinue because of a lack of efficacy or AE were censored.

3. Results

3.1. Patients

The trial was conducted from May 2011 to April 2019 across 167 sites in North America, Western Europe, Eastern Europe, Latin America, and Asia. A total of 767 patients were enrolled (384 from Europe); 91/105 (86.7%) randomized patients from the N01258 trial and 676/768 (88.0%) from the N01358 trial entered this LTFU trial. The Overall SS included 766 (99.9%) patients, of whom 753 had focal seizures and 13 had generalized-onset seizures. Overall, 368/766 (48.0%) patients completed the trial (patients who remained in the trial until termination or transitioned to another BRV trial, access program, or commercial BRV were considered trial completers). Three hundred and ninety-eight (52.0%) patients discontinued, due to lack of efficacy (164 [21.4%]), AE (96 [12.5%]), patient choice (89 [11.6%]), loss to follow-up (22 [2.9%]), or other reasons (27 [3.5%]). Patients had a mean age of 40.0 years (standard deviation [SD]: 12.9); 19 (2.5%) were 18 years of age or younger, 722 (94.3%) were over 18 but less than 65 years of age, and 25 (3.3%) were at least 65 years of age. Three hundred and ninety-six (51.7%) patients were female.

The Focal Seizures ES comprised 749 patients with a mean age at time of first seizure of 17.5 (SD: 13.6) years, and a mean duration of epilepsy of 22.7 (SD: 13.9) years. Three hundred and forty-eight (46.5%) patients had received five or more previous AEDs (taken at any time during the patient's lifetime and discontinued before entry into the previous trial; Table 1). Among 722 patients with evaluable data, the median (range) Baseline focal seizure frequency/28 days was 9.7 (0–710).

Table 1
Baseline[a] epilepsy characteristics.

Characteristic	Focal Seizures ES[b] (*N* = 749)
Age at time of first seizure, mean (SD), years	17.5 (13.6)
Epilepsy duration[c], mean (SD), years	22.7 (13.9)
Focal seizure frequency/28 days, median (range)	9.7 (0–710)[d]
Seizure types experienced during Baseline[e], *n* (%)	
Focal (partial-onset)	713 (95.2)
Focal aware (simple partial)	289 (38.6)
Focal impaired awareness (complex partial)	584 (78.0)
Focal to bilateral tonic-clonic (partial evolving to secondary generalized)	184 (24.6)
Generalized-onset seizures	5 (0.7)
Absence	2 (0.3)
Tonic	1 (0.1)
Tonic-clonic	3 (0.4)
Number of previous AEDs[f], *n* (%)	
0–1	151 (20.2)
2–4	250 (33.4)
≥5	348 (46.5)
Concomitant AEDs[g] taken by ≥10% of patients, *n* (%)	
Carbamazepine	282 (37.7)
Lamotrigine	199 (26.6)
Lacosamide	158 (21.1)
Oxcarbazepine	129 (17.2)
Topiramate	124 (16.6)
Valproic acid	89 (11.9)

AED, antiepileptic drug; ES, Efficacy Set; SD, standard deviation.
[a] Baseline refers to data collected at the time of entry into the previous trials.
[b] Patients with focal seizures from the N01358 and N01258 trials.
[c] Relative to date of first seizure.
[d] *n* = 722.
[e] Seizure types are listed per the International League Against Epilepsy (ILAE) 2017 classification [25], with the old terminology (ILAE 1981) in parentheses [26].
[f] AEDs taken at any time during the patient's lifetime and discontinued before entry into the previous trial.
[g] AEDs which were taken during brivaracetam treatment in the current trial, regardless of start and stop date.

3.2. Exposure to BRV

The total duration of BRV exposure (Overall SS) was 1932.9 patient-years (Table S2). Nearly half of the patients (323 [42.2%] patients) had at least 36 months of exposure to BRV. The most common modal dose of BRV was 200 mg/day (494 [64.5%] patients).

Kaplan–Meier-estimated retention rates are presented up to 36 months, due to the relatively low proportion of patients remaining in the trial beyond this time point (<42.2%). Kaplan–Meier-estimated retention was 71.9% (95% confidence interval: 68.6–75.0) at 12 months, 62.1% (58.6–65.5) at 24 months, and 53.7% (50.1–57.2) at 36 months (Fig. 1). The Kaplan–Meier-estimated proportion of patients that did not discontinue due to lack of efficacy or TEAE was 79.4% (76.2–82.1) at 12 months, 71.6% (68.1–74.7) at 24 months, and 66.0% (62.3–69.4) at 36 months (Fig. 1).

3.3. Safety and tolerability

3.3.1. Treatment-emergent adverse events

In the Overall SS (*N* = 766), TEAEs were reported by 643 (83.9%) patients, most commonly (≥10% of patients) headache (104 [13.6%] patients) and dizziness (100 [13.1%] patients) (Table 2). Treatment-emergent adverse events were reported by 440/529 (83.2%) patients randomized to BRV in the previous trials, and 203/237 (85.7%) patients previously randomized to PBO. Dizziness was more common in patients randomized to PBO in the previous trials than in those randomized to BRV (45 [19.0%] patients vs 55

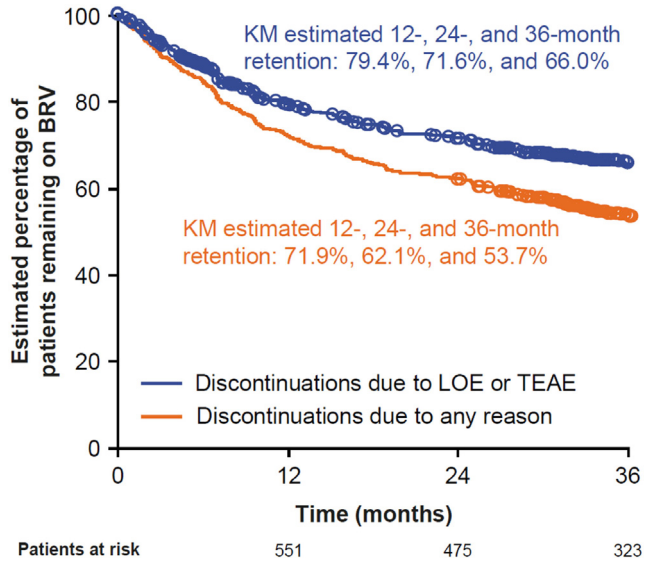

Fig. 1. Kaplan–Meier estimates of time to BRV discontinuation due to any reason, and due to lack of efficacy or TEAE[a] (Overall SS). Patients who permanently discontinued BRV were analyzed as events on the last day of treatment with BRV. Patients who completed the trial were censored on the last day of treatment with BRV. [a]Patients who did not discontinue due to lack of efficacy or TEAE were censored. BRV, brivaracetam; KM, Kaplan–Meier; LOE, lack of efficacy; SS, Safety Set; TEAE, treatment-emergent adverse event.

Table 2
Incidence of treatment-emergent adverse events.

Patients, *n* (%)	Overall SS[a] (*N* = 766)
Any TEAE	643 (83.9)
Drug-related TEAEs[b]	257 (33.6)
Serious TEAEs	140 (18.3)
Drug-related serious TEAEs[b]	18 (2.3)
Severe TEAEs	117 (15.3)
Permanent discontinuation of BRV due to TEAEs	91 (11.9)
Deaths	5 (0.7)
TEAEs reported by ≥5% of patients overall (MedDRA v15.0 preferred term)	
Headache	104 (13.6)
Dizziness	100 (13.1)
Somnolence	73 (9.5)
Nasopharyngitis	65 (8.5)
Upper respiratory tract infection	59 (7.7)
Fatigue	59 (7.7)
Urinary tract infection	58 (7.6)
Convulsion[c]	50 (6.5)
Back pain	47 (6.1)
Depression	46 (6.0)
Contusion	46 (6.0)
Fall	45 (5.9)
Anxiety	43 (5.6)
Arthralgia	41 (5.4)
Influenza	40 (5.2)
Drug-related TEAEs reported by ≥5% of patients overall (MedDRA v15.0 preferred term)	
Somnolence	49 (6.4)
Dizziness	41 (5.4)

MedDRA, Medical Dictionary for Regulatory Activities; SS, Safety Set; TEAE, treatment-emergent adverse event.
[a] Patients from the N01358 and N01258 trials.
[b] Relationship to brivaracetam as assessed by the investigator.
[c] Recorded as TEAEs 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.

[10.4%], respectively), though incidences of other TEAEs were similar for both groups. Overall, the incidence of TEAEs was higher in the first 3 months of the trial (402 [52.5%] patients) than in subsequent 3-month intervals (range: 18.2–31.1%) (Fig. S1). The incidence of TEAEs in the first 3 months was 266/529 (50.3%) in patients previously randomized to BRV and 136/237 (57.4%) in patients previously randomized to PBO; fatigue, dizziness, and somnolence were each slightly more common in patients that were on PBO in the previous trials (21 [8.9%] patients vs 15 [2.8%], 27 [11.4%] vs 20 [3.8%], and 22 [9.3%] vs 23 [4.3%], respectively; data shown for differences of ≥5%).

A total of 257 (33.6%) patients had TEAEs that were considered drug-related by the investigator. The most common drug-related TEAEs (≥5% of patients) were somnolence (49 [6.4%] patients) and dizziness (41 [5.4%] patients). A total of 140 (18.3%) patients reported at least one serious TEAE (considered drug-related in 18 patients). Serious TEAEs reported by ≥1% of patients overall were convulsion (15 [2.0%] patients; considered drug-related in 3 patients) and status epilepticus (11 [1.4%] patients; considered drug-related in 1 patient). Permanent discontinuation of BRV due to TEAEs occurred in 91 (11.9%) patients, most commonly (≥1% of patients) due to convulsion (12 [1.6%] patients), somnolence (8 [1.0%]), and pregnancy (8 [1.0%]). None of the pregnancies were considered BRV-related. One of the eight pregnancies occurred in a patient who was on oral hormonal contraceptives (BRV dose at the time: 200 mg/day); none of the other seven pregnancies occurred in patients who were on oral, injectable, or implantable hormonal contraceptives. Discontinuation of BRV due to TEAEs occurred in 57/529 (10.8%) patients randomized to BRV in the previous trials, and 34/237 (14.3%) patients randomized to PBO.

Overall, 194 (25.3%) of patients reported psychiatric TEAEs, most commonly (≥5% of patients) depression (46 [6.0%] patients) and anxiety (43 [5.6%]). Psychiatric TEAEs led to BRV discontinuation in 26 (3.4%) patients. Drug-related psychiatric TEAEs were reported by 63 (8.2%) patients; those reported by ≥1% of patients overall were depression (12 [1.6%] patients), anxiety (9 [1.2%] patients), and insomnia (9 [1.2%] patients). Overall, 51 (6.7%) patients reported TEAEs potentially associated with behavioral disorders; the only behavioral TEAE reported by ≥1% of patients was irritability (33 [4.3%] patients). Irritability was considered to be drug-related in 22 (2.9%) patients. One hundred and nine (14.2%) patients reported TEAEs potentially associated with suicidality or suicidal ideation; those reported by ≥1% of patients were depression (46 [6.0%]), laceration (26 [3.4%]), suicidal ideation (19 [2.5%]), and depressed mood (8 [1.0%]). Suicidal ideation and depressed mood were considered to be drug-related in three (0.4%) patients and one (0.1%) patient, respectively; none of the cases of laceration were considered drug-related. Seven (0.9%) patients had failed suicide attempts, of whom two (0.3%) had suicide attempts that were considered to be BRV-related.

Five deaths (0.7% of patients) were reported, all of which occurred in the Post-Treatment Period. All five deaths were reported in patients with focal seizures. One patient died due to a serious TEAE of intentional overdose with lamotrigine, one due to myocardial infarction, one due to cardiorespiratory arrest (the patient had exertional dyspnea on the same day, and had previously been diagnosed with and treated for thymoma), and one due to head injury; none of these TEAEs were considered BRV-related. One patient died due to serious TEAEs of hypoplastic anemia and pneumonia (neither TEAE was considered drug-related). This patient also had several nonserious TEAEs which were reported as having a fatal outcome: focal aware (simple partial) seizures (reported as changes in seizure type from IA1 to IA2; considered BRV-related), somnolence (considered BRV-related), and weight decreased (not considered BRV-related).

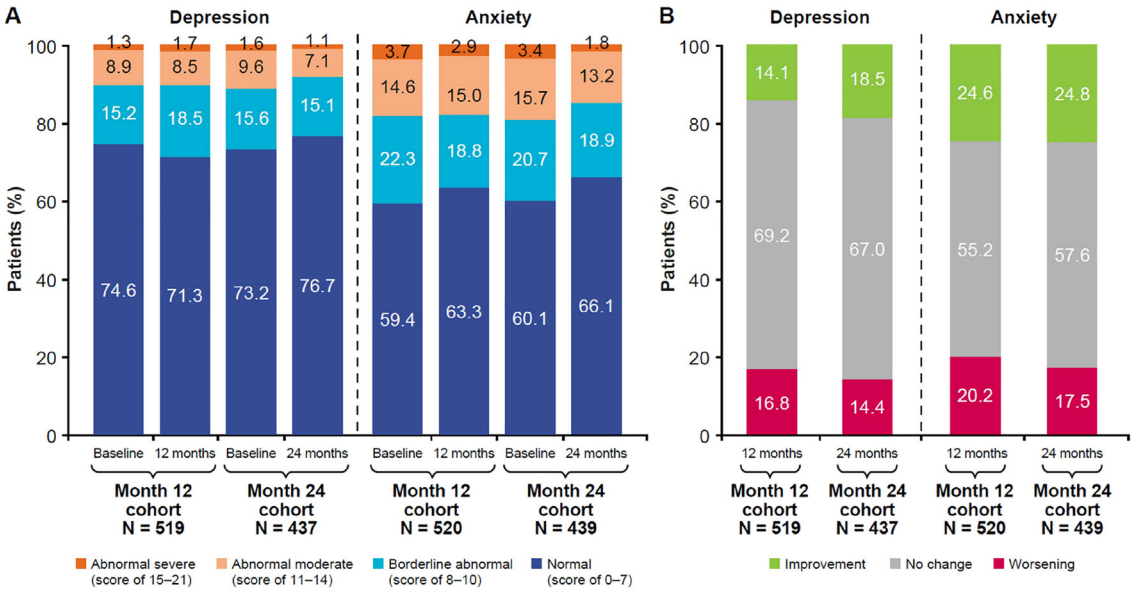

Fig. 2. Hospital Anxiety and Depression Scale scores. (A) Proportion of patients in each score category at Baseline and follow-up; (B) proportion of patients with improvements, no change, or worsening in category from Baseline; Overall SS. Monthly cohorts define groups of patients who have completed the scheduled visit at the time point defined by the cohort (e.g., 24-Month Cohort includes patients who completed the scheduled visit at the end of year 2). SS, Safety Set.

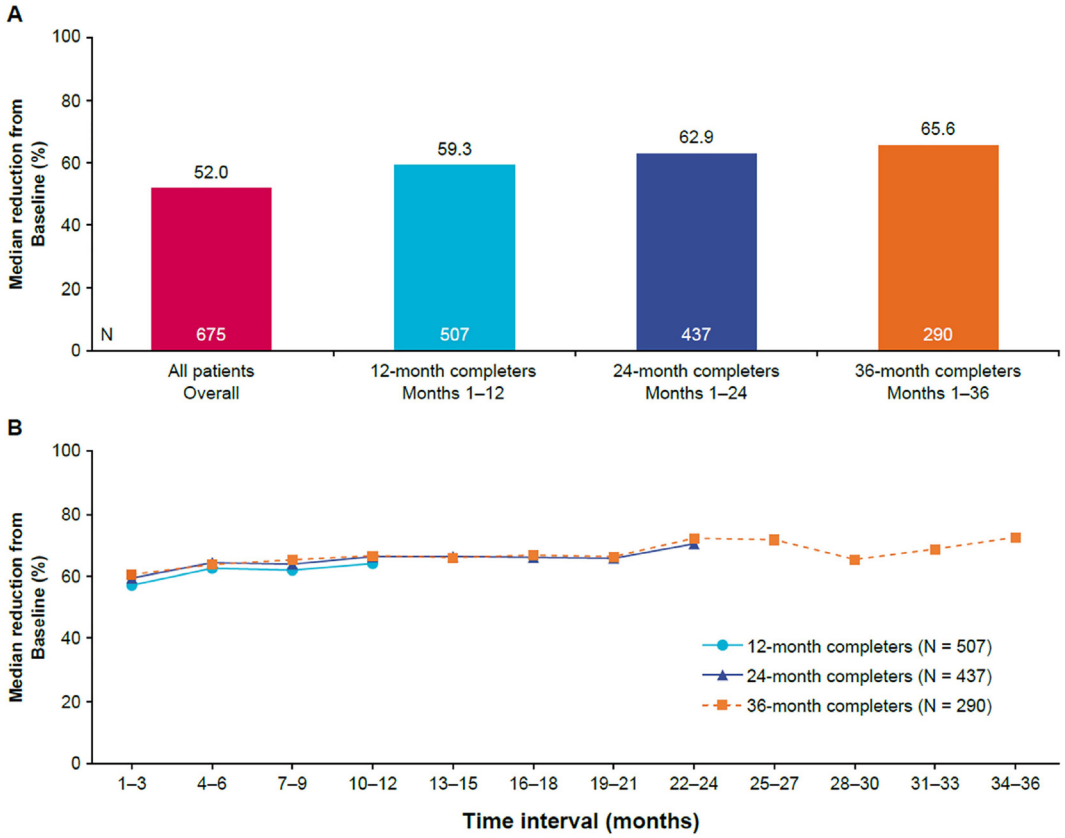

Fig. 3. Percentage reduction in focal seizure frequency from Baseline of previous trial (Focal Seizures ES[a]) in all patients and by yearly completer cohorts. (A) Overall and (B) in 3-month time intervals. Data are presented up to 36 months, because of a relatively low proportion of patients remaining in the trial beyond this time point. Completer cohorts include patients who completed at least the specified duration of brivaracetam exposure. [a]Patients with focal seizures from the N01358 trial. ES, Efficacy Set.

The incidences of TEAEs in the subgroups of patients with focal seizures and generalized-onset seizures are given in Table S3.

3.3.2. Other safety outcomes

No clinically relevant findings were observed for any mean changes from Baseline in laboratory tests, vital signs, body weight, or ECGs.

At Baseline, HADS data were reported for 751/766 (98.0%) patients in the Overall SS; 559/751 (74.4%) patients had a normal depression score, 443/751 (59.0%) had a normal anxiety score, and 392/751 (52.2%) patients had normal scores for both depression and anxiety. 78/751 (10.4%) patients had an abnormal depression score, 144/751 (19.2%) patients had an abnormal anxiety score, and 37/751 (4.9%) had abnormal scores for both depression and anxiety. Hospital Anxiety and Depression Scale scores for depression were generally stable from Baseline to 12 and 24 months (Fig. 2A). Most patients had no change in depression category at 12 (69.2% [359/519]) or 24 months (67.0% [293/437]) (Fig. 2B). For anxiety scores, the proportion of patients with "normal" anxiety was numerically higher at 24 months (Fig. 2A). Furthermore, a numerically higher proportion of patients had improvement in anxiety category compared with the proportion that had worsened at 24 months, though most patients (55.2% [287/520] at 12 months; 57.6% [253/439] at 24 months) had no change in category (Fig. 2B).

3.4. Efficacy

3.4.1. Seizure assessments

Results for efficacy outcomes are presented up to 36 months, due to the relatively low proportion of patients remaining in the trial beyond this time point (<42.2%). Changes in seizure frequency and 50% responder rate were analyzed in patients in the Focal Seizures ES from the N01358 trial only ($N = 675$). The overall median percentage reduction (Q1, Q3) from Baseline to the Evaluation Period in focal seizure frequency/28 days was 52.0% (16.8, 81.5) (Fig. 3A). Patients completing 12 months of treatment ($N = 507$) had a median (Q1, Q3) percentage reduction in focal seizure frequency of 59.3% (26.6, 84.9), and those completing 36 months ($N = 290$) had a median (Q1, Q3) percentage reduction of 65.6% (33.9, 86.5). The median percentage reduction in focal seizure frequency was generally sustained over time in each completer cohort (Fig. 3B). The 50% responder rate was 51.7% (349/675) overall, 60.0% (304/507) in patients who completed at least 12 months of treatment, and 63.4% (184/290) in patients who completed 36 months (Fig. 4A). The 50% responder rate was generally stable over time in each completer cohort (Fig. 4B).

Seizure freedom was analyzed in patients in the Focal Seizures ES (including those from the N01258 and N01358 trials) ($N = 642$). Continuous seizure freedom for 6 and 12 months was achieved in 26.0% (167/642) and 17.9% (115/642) of patients, respectively (Fig. 5). In patients who completed 12 months of treatment, continuous seizure freedom for 6 and 12 months was 17.8% (97/544) and 6.3% (34/544), respectively. In patients who completed 36 months of treatment, continuous seizure freedom for 6 and 12 months was 29.5% (94/319) and 18.2% (58/319), respectively.

No seizure freedom assessments are presented for the Generalized Seizures ES, due to the small number of patients ($N = 11$).

3.4.2. Patient Weighted Quality of Life in Epilepsy Questionnaire 31

In the Focal Seizures ES, overall mean changes from Baseline to 12 and 24 months in total score and subscale scores for

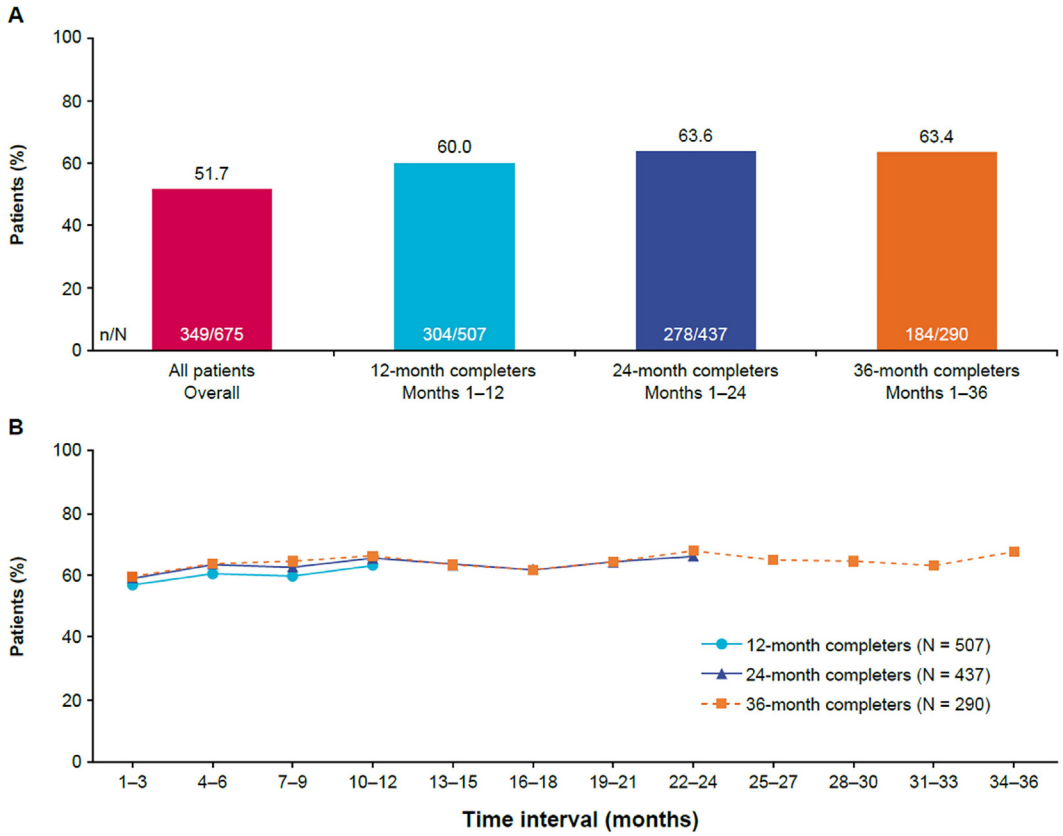

Fig. 4. Fifty percent responder rate for focal seizure frequency from Baseline of previous trial (Focal Seizures ES[a]) in all patients and by yearly completer cohorts. (A) Overall and (B) in 3-month time intervals. Data are presented up to 36 months, because of a relatively low proportion of patients remaining in the trial beyond this time point. Completer cohorts include patients with at least the specified duration of brivaracetam exposure. [a]Patients with focal seizures from the N01358 trial. ES, Efficacy Set.

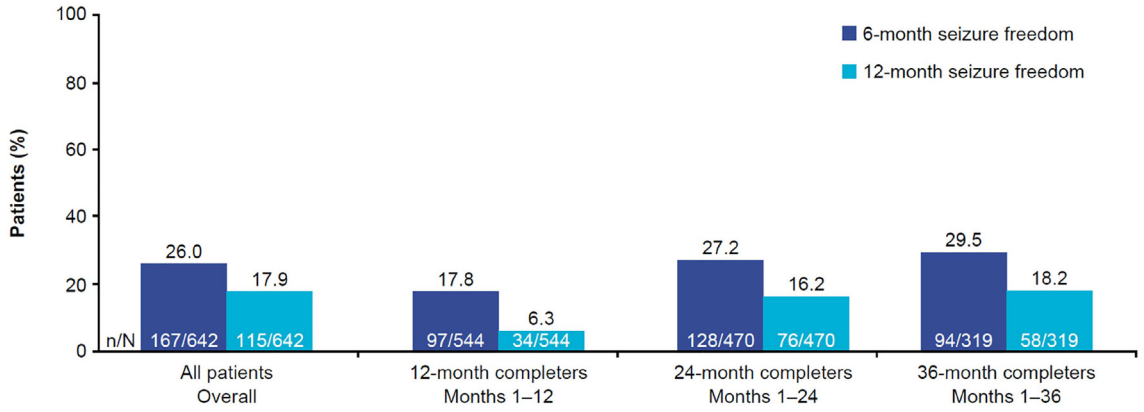

Fig. 5. Continuous seizure freedom for ≥6 months and ≥12 months in patients with focal seizures (Focal Seizures ES)[a]. Data are presented up to 36 months, because of a relatively low proportion of patients remaining in the trial beyond this time point. Completer cohorts include patients with at least the specified duration of brivaracetam exposure. Patients were considered to have 6- or 12-month seizure freedom if they reported no seizures during brivaracetam treatment for 6 or 12 months at any time during the cohort interval, and the seizure diary was completed for at least 90% of days within the seizure-free interval. Patients whose duration of brivaracetam treatment was less than the duration of seizure freedom were failures for seizure freedom. [a]Patients with focal seizures from the N01358 and N01258 trials. ES, Efficacy Set.

QOLIE-31-P are shown in Fig. 6A, and the proportion of patients with clinically meaningful improvement (based on predefined cut-offs) is shown in Fig. 6B. For the total score, 42.4% (216/510) of patients at 12 months and 46.8% (207/442) of patients at 24 months reported clinically meaningful improvement (Fig. 6B). For the subscales (seizure worry, daily activities/-

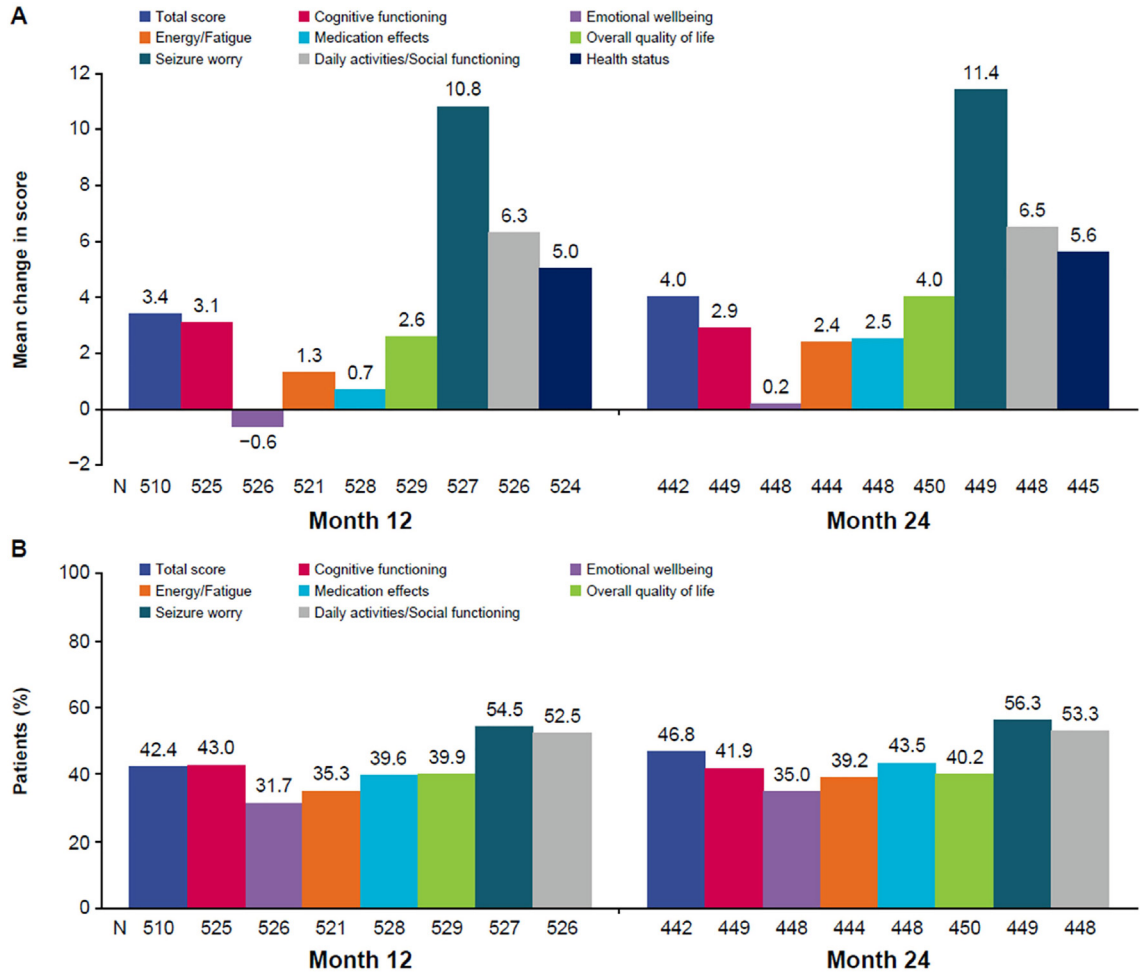

Fig. 6. Patient Weighted Quality of Life in Epilepsy Questionnaire 31 scores. (A) Change from Baseline[a]; (B) proportion of patients with clinically meaningful improvement[b]; Focal Seizures ES[c]. Only patients with a nonmissing change from Baseline values are summarized at each time point. Scores range from 0 to 100 with higher scores corresponding to better functioning/health status. [a]Defined as the levels taken from the previous trial, before any exposure to brivaracetam. [b]Clinically meaningful improvement was defined as the following changes from Baseline [15]: Total Score 5.19; Cognitive Functioning 5.34; Emotional wellbeing 4.76; Energy/Fatigue 5.25; Medication Effects 5.00; Overall Quality of Life 6.42; Seizure Worry 7.42; Daily Activities/Social Functioning 3.95. [c]Patients with focal seizures from the N01358 and N01258 trials. ES, Efficacy Set.

social functioning, cognitive functioning, emotional wellbeing, energy/fatigue, medication effects and overall quality of life), the proportion of patients with clinically meaningful improvement ranged from 31.7% to 54.5% at 12 months and from 35.0% to 56.3% at 24 months, with the numerically highest improvements occurring in the seizure worry and daily activities/social functioning subscales (Fig. 6B).

4. Discussion

The long-term safety and tolerability profile of adjunctive BRV treatment in this open-label LTFU trial was consistent with the known safety and tolerability profile of BRV in patients with focal seizures.

Per the entry criteria of the previous double-blind trials, patients had uncontrolled epilepsy despite treatment with one to two concomitant AEDs. Ninety-one of one hundred and five (86.7%) randomized patients from the N01258 trial and 676/768 (88.0%) randomized patients from the N01358 trial continued into this LTFU trial. Patients in the LTFU trial had a long epilepsy duration, a high seizure frequency at Baseline, and nearly half had received five or more previous AEDs. Total exposure to BRV was 1932.9 patient-years. Most patients received a modal dose of 200 mg/day of BRV. The duration of treatment for individual patients was affected by external factors, including the commercial availability of BRV, and was therefore shorter than expected. In many countries, the trial was closed when BRV became commercially available for the adjunctive treatment of focal seizures.

Open-label extensions of trials in other AEDs, including perampanel, zonisamide, and lacosamide, have included double-blind transition periods during which the study medication was titrated to an individual maximum tolerated dose or predefined target dose, either in all patients or in patients originally randomized to PBO [16–18]. In this LTFU trial, there was no titration period. Patients from the N01358 trial started at a BRV dose of 150 mg/day and patients from the N01258 trial at a BRV dose of 200 mg/day, regardless of whether they were randomized to BRV 100 mg/day, BRV 200 mg/day, or PBO in those trials. BRV treatment was started directly without blinding and on an effective dose, with further dose adjustments during the LTFU trial as needed.

We assessed long-term retention on adjunctive BRV from the first BRV dose during LTFU (regardless of whether patients received BRV or PBO in the double-blind trials). A previous analysis assessed retention from first exposure to BRV (either in the N01358 trial, or during LTFU in the N01379 trial). Although the data are not directly comparable, Kaplan–Meier-estimated 12- and 36-month retention was similar (70.8% and 52.3%, respectively, versus 71.9% and 53.7% in the current analysis) [19]. Kaplan–Meier-estimated retention on adjunctive BRV from first BRV exposure has also been investigated in pooled analyses of long-term data covering phase IIb/III core trials (including N01258 and N01358) and interim data from their corresponding LTFU studies (including N01379) [20,21]. Twelve-month retention on BRV in the current trial (71.9%) was similar to that reported in the pooled analyses (52 weeks: 69.8%) [21]. The Kaplan–Meier-estimated proportions of patients not discontinuing because of lack of efficacy or TEAE in the current trial (79.4% and 71.6% at 12 and 24 months, respectively) were also similar to those reported previously (79.8% and 68.1%, respectively) [20].

The overall incidences of TEAEs (83.9%) and discontinuation due to TEAEs (11.9%) were in line with the analysis of pooled data from trials of adjunctive BRV, in which 84.5% of patients reported TEAEs and 12.1% discontinued due to TEAEs [20]. The incidence of TEAEs was highest in the first 3 months of treatment, with a slightly higher incidence in patients previously randomized to PBO versus BRV (57.4% vs 50.3%). These findings could be due to the design of this LTFU trial, as most of the patients either changed their BRV dose or switched directly from PBO to an effective BRV dose.

Psychiatric TEAEs are of particular concern in patients with epilepsy, in whom the prevalence of psychiatric comorbidities is considerably higher than that in the general population; a meta-analysis showed that 23.2% of patients with epilepsy had suicidal ideation and 7.4% had suicide attempts [22]. In this trial, there was a low incidence of drug-related psychiatric TEAEs. BRV-related depression, suicidal ideation, and suicide attempt were reported by 12 (1.6%), 3 (0.4%), and 2 (0.3%) patients, respectively. A relatively high proportion of patients had normal HADS scores for anxiety or depression at Baseline. Furthermore, depression scores were generally stable through the first 2 years of the Evaluation Period, with most patients having no change in depression category. A numerical improvement from Baseline in the proportion of patients with normal scores for anxiety was observed at 24 months. A previous LTFU trial of adjunctive BRV reported numerical decreases (indicating improvement) in anxiety scores at 24 months; depression scores were unchanged at last value in all patients assessed, with minor decreases observed over time in the completer cohorts [23]. That analysis was based on overall mean changes in score, rather than the proportion of patients in each score category.

Patients with focal seizures who remained in this LTFU trial reported sustained seizure frequency reduction from Baseline to 36 months. Overall, median percentage reduction in focal seizures was 52.0%. Approximately half (51.7%) of all patients with focal seizures were 50% responders; analyses by 3-month time intervals showed that 50% responder rates were relatively stable in patients completing 12, 24, and 36 months of treatment. The previous analysis of long-term data reported a similar 50% responder rate for focal seizures (48.7%) [20]. Efficacy results are in line with a similar LTFU trial of adjunctive BRV, in which median reduction from Baseline in focal seizure frequency/28 days was 57.3%, 50% responder rate was 55.6%, and continuous 6- and 12-month seizure freedom rates were 30.3% and 20.3%, respectively [23]. In the current trial, 26.0% of patients with focal seizures were seizure-free for at least 6 months and 17.9% were seizure-free for at least 12 months. As anticipated, given the longer time intervals assessed, patients in the 24- and 36-month completer cohorts had higher 6- and 12-month continuous seizure freedom rates than those in the 12-month completer cohort.

Results for the QOLIE-31-P assessments showed that 42.4% of patients at 12 months and 46.8% of patients at 24 months had clinically meaningful improvements in total score, based on previously defined minimally important changes [15], in line with an analysis of long-term data [20]. In both analyses, seizure worry and daily activities/social functioning were the subscales in which the highest proportion of patients had a meaningful improvement. An analysis of pooled data from three BRV trials (including N01258 and N01358) found improvements in QOLIE-31-P subscales that are sensitive to efficacy, including seizure worry [24]. Another LTFU trial of adjunctive BRV reported improvement in QOLIE-31-P total scores, based on mean changes from Baseline of 5.7 at 12 months and 6.5 at 24 months [23]. Similarly, the results of this trial showed mean improvements of 3.4 and 4.0 in total score at 12 and 24 months, respectively.

This study had several limitations. The open-label trial design meant that no comparator or PBO was included. With the exception of patients who received PBO during the previous trials, patients entering LTFU were continuing on BRV and thus represent a select group in which initial BRV treatment was most likely effective and well tolerated. Furthermore, efficacy data from long-term trials should be interpreted with caution, given a potential selection bias for treatment responders over time as

patients with a poorer response to trial medication discontinue. Finally, no meaningful conclusions could be drawn regarding the tolerability and efficacy of BRV in the subgroup of patients with generalized-onset seizures given the small sample size.

5. Conclusions

This LTFU trial provides long-term safety data for adjunctive BRV administered at flexible dose (up to 200 mg/day) for up to approximately 8 years. BRV was generally safe and well tolerated; results were consistent with the known safety profile for BRV. Retention on BRV was relatively high. Results indicate the long-term efficacy of BRV in this select group of patients with focal seizures who entered the LTFU trial. These observations provide additional evidence for the use of adjunctive BRV for the long-term treatment of patients with focal seizures.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Manuel Toledo has received grants and consultation honoraria from Arvelle Therapeutics, Bial, Eisai, Esteve, Exeltis, GW Pharmaceuticals, Sanofi, and UCB Pharma. Christian Brandt has received personal compensation from Arvelle Therapeutics, Desitin, Eisai, GW Pharmaceuticals, Idorsia, and UCB Pharma for consulting services or speaking activities. Anne-Liv Schulz, Jody M. Cleveland, and Gilbert Wagener are employees of UCB Pharma. Pavel Klein has served as a consultant for Abbott and Arvelle Therapeutics, a speaker for Sunovion, a consultant and speaker for Aquestive Therapeutics, Eisai, Neurelis, SK Life Science, and UCB Pharma, is a member of the Medical Advisory Board for Alliance/Stratus and of the Scientific Advisory Board for OB Pharma, and has received research support from Lundbeck. Pier Paolo Quarato has no conflicts of interest to disclose.

Data statement

Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the United States 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. Before 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 implemented. All documents are available in English only, for a prespecified time, typically 12 months, on a password protected portal.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2021.107897.

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