Received: 18 November 2019 | Revised: 27 February 2020 | Accepted: 2 March 2020

DOI: 10.1111/epi.16484

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: An up to 11-year, open-label, follow-up trial

Terence J. O'Brien[1,2] | **Simon Borghs**[3] | **Qin (Jane) He**[4] | **Anne-Liv Schulz**[5] | **Stephen Yates**[4] | **Victor Biton**[6]

[1]Department of Neuroscience, Central Clinical School, Alfred Health, Monash University, Melbourne, Victoria, Australia

[2]Departments of Medicine and Neurology, Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

[3]UCB Pharma, Slough, UK

[4]UCB Pharma, Raleigh, North Carolina

[5]UCB Pharma, Monheim am Rhein, Germany

[6]Clinical Trials Inc, Little Rock, Arkansas

Correspondence
Terence J. O'Brien, Department of Neuroscience, Central Clinical School, Monash University, Alfred Centre, Level 6, 99 Commercial Rd, Melbourne, Victoria 3004, Australia.
Email: terence.obrien@monash.edu

Funding information
UCB Pharma

Abstract

Objective: To evaluate long-term safety/tolerability of brivaracetam at individualized doses ≤200 mg/d (primary) and maintenance of efficacy over time (secondary) in adults with focal seizures or primary generalized seizures (PGS) enrolled in phase 3, open-label, long-term follow-up trial N01199 (NCT00150800).

Methods: Patients ≥16 years of age who had completed double-blind, placebo-controlled adjunctive brivaracetam trials NCT00175825, NCT00490035, NCT00464269, or NCT00504881 were eligible. Outcomes included safety, efficacy, and quality of life.

Results: The safety set included 667 patients (focal seizures, 97.8%; PGS, 2.2%); the efficacy set included 648 patients with focal seizures and 15 patients with PGS. Overall, 49.2% of patients had ≥48 months of exposure. Treatment-emergent adverse events (TEAEs) occurred in 91.2% of all patients (91.3% of focal seizures group), brivaracetam discontinuation due to TEAEs in 14.8%, drug-related TEAEs in 56.7%, and serious TEAEs in 22.8%. The most common TEAEs in the focal seizures group (≥15%) were headache (25.3%) and dizziness (21.9%). Mean changes from baseline in Hospital Anxiety and Depression Scale scores at last value during 2-year evaluation were −0.7 (standard deviation [SD] = 4.3) and −0.2 (SD = 4.4) overall. In the focal seizures group, median reduction from baseline in focal seizure frequency/28 days was 57.3%, 50% responder rate was 55.6%, and 6-month and 12-month seizure freedom rates were 30.3% and 20.3%, respectively. Efficacy outcomes improved by exposure duration cohort and then stabilized through the 108-month cohort. Mean improvement from baseline in Patient-Weighted Quality of Life in Epilepsy Inventory total score (efficacy set) was 5.7 (SD = 16.1, Cohen's $d = 0.35$) at month 12 and 6.5 (SD = 18.0, Cohen's $d = 0.36$) at month 24.

Significance: Adjunctive brivaracetam was well tolerated, with a good safety profile in long-term use in adults with epilepsy at individualized doses. Approximately half of the patients remained in the trial at 4 years. Brivaracetam reduced focal seizure

frequency versus baseline. Efficacy improved with increasing exposure duration and remained stable through the 9-year cohort.

KEYWORDS

antiepileptic drug, focal seizure, hospital anxiety and depression scale, primary generalized seizure, seizure control, tolerability

1 | INTRODUCTION

Brivaracetam is a high-affinity synaptic vesicle protein 2A ligand indicated for the treatment of focal (partial-onset) seizures. In the USA, brivaracetam has been approved as adjunctive therapy and monotherapy for patients ≥4 years of age (oral formulations only; brivaracetam injection is currently only indicated for patients ≥16 years of age)[1]; in the European Union and in Australia, brivaracetam has been approved as adjunctive therapy for patients ≥4 years of age.[2-4]

As antiepileptic drug (AED) treatment is usually chronic and may be lifelong, it is important that the safety, tolerability, and efficacy of the drug is maintained long-term. A pooled analysis of data from phase 2b, phase 3, and long-term follow-up trials in adults with uncontrolled focal seizures showed that adjunctive brivaracetam (5-200 mg/d) was effective and generally well tolerated when administered long-term (≥8.0 years).[5] In addition, health-related quality of life improved.

Here, we report the findings of an open-label, multinational, follow-up trial conducted to evaluate long-term safety, tolerability, and efficacy of adjunctive brivaracetam at individualized doses up to 200 mg/d (N01199; ClinicalTrials.gov: NCT00150800). N01199 enrolled patients 16 years of age and older with epilepsy who completed the double-blind, placebo-controlled trials of adjunctive brivaracetam N01193, N01252, N01253, and N01254. The primary objective was to evaluate long-term safety and tolerability of brivaracetam. The maintenance of efficacy over time was investigated as a secondary objective.

Key Points

- Up to 11-year, open-label, follow-up trial of adjunctive brivaracetam at individualized doses in adult patients with focal seizures or primary generalized seizures
- Adjunctive brivaracetam therapy was well tolerated with a good safety profile in adults with epilepsy at individualized doses up to 200 mg/d
- Approximately half of the patients remained in the trial at 4 years
- Overall, 55.6% of patients with focal seizures experienced ≥50% reduction in focal seizure frequency; 30.3% experienced continuous seizure freedom for ≥6 months
- Efficacy outcomes improved with increasing duration of brivaracetam exposure, with changes remaining stable through the 9-year cohort

2 | MATERIALS AND METHODS

2.1 | Trial design

This was a phase 3, multicenter, open-label, flexible-dose, uncontrolled, long-term follow-up trial of adult patients with focal seizures, with or without secondary generalization, or primary generalized seizures (PGS). Among the core trials from which patients were recruited, N01193 (NCT00175825),[6] N01252 (NCT00490035),[7] and N01253 (NCT00464269)[8] evaluated fixed doses of brivaracetam, whereas N01254 (NCT00504881)[9] was a flexible-dose trial (Table S1). All of these trials enrolled drug-resistant patients. The trials were all multinational but varied in the specific countries involved.

The current trial was conducted from January 2006 to September 2017 at 99 sites across Australia, Brazil, Canada, India, Mexico, and the USA. For each patient, this trial ran throughout the duration of the clinical development period of brivaracetam, and continued until marketing authorization for brivaracetam was granted by any health authority in an indication of adjunctive treatment in adults with drug-resistant focal seizures (whether or not secondarily generalized), until UCB Pharma closed the trial, until patients transitioned to another brivaracetam trial, or until a managed access program, named patient program, compassionate use program, or similar type of access program was established as allowed per country-specific requirement in addition to legal and regulatory guidelines.

The trial protocol, amendments, and patient informed consents were reviewed and approved by a national or regional independent ethics committee or institutional review board.

The trial was conducted in accordance with International Council for Harmonization–Good Clinical Practice, the Declaration of Helsinki, and local laws of the countries involved. All patients provided written informed consent before enrollment.

2.2 | Patient population

Male or female patients ≥16 years of age who had completed the core trials listed in Table S1 and were expected by the investigator to benefit from long-term brivaracetam administration were eligible. The trials N01193, N01252, and N01253 enrolled patients with focal seizures with or without secondary generalization, whereas N01254 enrolled patients with focal seizures and also a smaller number of patients with PGS.

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 brivaracetam trial. Women who were pregnant, lactating, or of childbearing potential and not using approved methods of contraception (unless sexually abstinent) were excluded.

2.3 | Treatment schedule

The starting dose for each patient in this long-term follow-up trial was the dose defined/reached at the end of the previous trial: 20 mg/d for patients from N01193, 50 mg/d for patients from N01252, 50 or 20 mg/d for patients from N01253, and up to 100 mg/d for patients from N01254. At each trial visit, if necessary, brivaracetam dosage could be uptitrated or reduced in 50 mg/d increments; the maximum dose was 200 mg/d. Patients who discontinued brivaracetam treatment entered a down-titration period with a last down-titration step of 20 mg/d for 1 week, which was followed by 2-4 weeks free of brivaracetam before the final visit.

Dose adjustment to concomitant AEDs may have been made at any time during the trial, and patients may have started new AEDs or discontinued concomitant AEDs.

Conversion to brivaracetam monotherapy was no longer permitted after a protocol amendment in June 2011; however, patients already on brivaracetam monotherapy were allowed to continue monotherapy treatment. The use of concomitant vigabatrin was prohibited.

Following the entry visit (month 0), which typically corresponded to the final visit of the previous trial, there were visits at months 1, 2, 3, and 6 for patients from N01252, N01253, and N01254, and visits at months 1, 2, 3, 4, 5, and 6 for patients from N01193. Subsequently, visits occurred every 3 months.

2.4 | Outcome measures

Primary safety variables included occurrence of treatment-emergent adverse events (TEAEs), serious TEAEs, and withdrawal due to TEAEs. Other safety variables were as follows: laboratory tests, vital signs, body weight, electrocardiogram (ECG), change in Hospital Anxiety and Depression Scale (HADS) scores[10] from the baseline of the previous trial to each assessment for the first 2 years and to the last evaluation period assessment during the first 2 years, and Columbia–Suicide Severity Rating Scale (C-SSRS).[11]

For patients with focal seizures, efficacy variables included the frequency of focal seizures per 28 days during the evaluation period, percentage reduction in 28-day focal seizure frequency from baseline of the previous trial to the evaluation period, and 50% responder rate (defined as patients with a ≥50% reduction in focal seizure frequency from the baseline period of the previous trial) over the evaluation period. Other efficacy variables included the proportion of patients with focal seizures continuously seizure-free for all seizure types for at least 6 months and at least 12 months during the evaluation period.

Additional efficacy variables included change in EuroQol-5 Dimensions Questionnaire (EQ-5D) responses and in Patient-Weighted Quality of Life in Epilepsy Inventory (QOLIE-31-P)[12] scores from baseline of the previous trial to each assessment for the first 2 years and to the last evaluation period assessment during the first 2 years. EQ-5D responses and QOLIE-31-P scores were evaluated for the overall trial population by time point in post hoc analyses.

2.5 | Statistical methods

Descriptive statistics were used to summarize safety and efficacy outcomes; no statistical hypothesis testing was planned. The safety set (SS) comprised all patients who took at least one dose of trial medication. The efficacy set (ES) included all patients who took at least one dose of trial medication and had at least one day with completed seizure daily record card during the evaluation period. As well as the overall ES, separate efficacy populations were defined for patients with focal seizures and patients with PGS.

The last value for HADS, EQ-5D, and QOLIE-31-P was the last assessment after the date of the first dose of brivaracetam and up to and including the visit at the end of year 2 and any early discontinuation visits for patients who did not complete through the visit at the end of year 2. The last value for clinical laboratory parameters, vital signs, and ECGs was the

last available result obtained after the first dose of brivaracetam and before or on the date of the last dose.

No sample size calculation was performed. Sample size depended on recruitment into and completion of the preceding trials.

3 | RESULTS

3.1 | Baseline patient demographics, characteristics, and concomitant AEDs

In total, 668 patients were enrolled in N01199; 667 (99.9%) were included in the SS (Table 1 and Figure S1). The majority of patients had focal seizures (652 [97.8%] patients from N01193, N01252, N01253, and N01254); 15 patients (2.2%) from N01254 presented with PGS. Due to the very small number of patients with PGS in this trial, the safety and tolerability results are presented for these patients but not the efficacy results. Overall, 171 (25.6%) patients completed the trial and 496 (74.4%) discontinued. Reasons for discontinuation were lack of efficacy (165 [24.7%] patients), adverse event (107 [16.0%] patients), patient's choice (90 [13.5%] patients), other (76 [11.4%] patients), and lost to follow-up (58 [8.7%] patients).

Conditions that resolved before entry into, or that were ongoing at the time of entry into the previous double-blind trial in ≥10% of SS patients were headache (162 [24.3%] patients), depression (97 [14.5%]), and vagal nerve stimulator implantation (74 [11.1%]). The mean duration of epilepsy at baseline was 21.6 years for patients with focal seizures and 16.6 years for patients with PGS (Table 1; focal seizure ES and PGS ES). As per the protocol, patients enrolled in the previous double-blind trials had to be taking one or two concomitant AEDs (N01193, N01252, N01253) or one to three concomitant AEDs (N01254) and doses were kept stable throughout the double-blind trials. Most patients received two concomitant AEDs at entry into the previous double-blind trials (Table 1). During the long-term extension trial, all patients in the focal seizure and PGS groups received at least one concomitant AED. The most commonly taken concomitant AEDs are presented in Table 1.

3.2 | Safety outcomes

3.2.1 | Brivaracetam exposure

The total duration of brivaracetam exposure during N01199 was 2965.1 patient-years for the SS (Table S2), including 2891.1 patient-years in the focal seizure group and 74.1 patient-years in the PGS group. Overall, approximately half of the patients (328 [49.2%]) had at least 48 months of exposure to brivaracetam and small proportions of patients remained in the trial at 108 months (83 [12.4%] patients), 120 months (51 [7.6%] patients), and 132 months (16 [2.4%] patients; Table S2). Among patients with focal seizures, 319 (48.9%) and 83 (12.7%) had at least 48 months and at least 108 months of exposure to brivaracetam, respectively; among patients with PGS, nine (60.0%) and four (26.7%) had at least 48 months and at least 102 months of exposure to brivaracetam, respectively. The most common modal dose of brivaracetam was 150 mg/d (228 [34.2%] patients); 194 (29.1%) patients had a modal dose of 50 mg/d, and 161 (24.1%) patients had a modal dose of 100 mg/d.

3.2.2 | Treatment-emergent adverse events

Overall, 608 (91.2%) patients reported at least one TEAE, including 595 (91.3%) patients with focal seizures (Table 2; SS). Permanent discontinuation of brivaracetam due to TEAEs occurred in 99 (14.8%) patients overall and in 96 (14.7%) patients with focal seizures. Occurrence of TEAEs was similar in the focal seizure and PGS groups, although no meaningful comparison could be made because of the low number of patients with PGS. The most commonly reported TEAEs in patients with focal seizures (≥15%) were headache (165 [25.3%] patients) and dizziness (143 [21.9%] patients). In the overall population, 13 (1.9%) patients discontinued brivaracetam because of pregnancy and eight (1.2%) because of suicidal ideation. No other TEAEs led to permanent discontinuation of brivaracetam in >1% of patients.

Psychiatric TEAEs were reported by 212 (31.8%) patients. The most commonly reported psychiatric TEAEs (≥5%) were depression (71 [10.6%] patients), insomnia (49 [7.3%] patients), and anxiety (45 [6.7%] patients). Psychiatric TEAEs led to discontinuation of brivaracetam in 34 (5.1%) patients. The only single psychiatric TEAE leading to discontinuation in ≥1% of patients was suicidal ideation (eight [1.2%] patients).

The overall incidence of TEAEs was highest in months 1-3 and diminished over time (Figure S2). The overall incidence of TEAEs was similar between patients who received placebo (77.8%) and brivaracetam (79.0%) in the placebo-controlled core trials. The incidences of dizziness (27.2% vs 19.6%), depression (14.2% vs 9.5%), and insomnia (10.5% vs 6.3%) were higher in patients who received placebo in the core trial and transitioned to brivaracetam in this trial than in those who received brivaracetam in the core trial.

3.2.3 | Drug-related TEAEs

Overall, drug-related TEAEs were reported by 378 patients (56.7%; Table 2; SS). The most common TEAEs considered

TABLE 1 Baseline[a] patient demographics, characteristics, and concomitant antiepileptic drugs[b] taken by ≥10% of patients in either trial group (SS, focal seizure ES, PGS ES)

Characteristic	Focal seizure, SS, n = 652	PGS, SS, n = 15
Age		
Mean (SD), y	34.4 (12.3)	30.7 (9.3)
Median (range), y	33.0 (16-70)	28.0 (19-50)
≤18 y, n (%)	51 (7.8)	0
19 to <65 y, n (%)	596 (91.4)	15 (100)
≥65 y, n (%)	5 (0.8)	0
Male, n (%)	354 (54.3)	10 (66.7)
Body mass index, mean (SD), kg/m^2	25.9 (6.6)[c]	22.9 (3.3)
	Focal seizure, ES, n = 648	**PGS, ES, n = 15**
Age at time of first seizure, mean (SD), y	13.2 (10.9)	14.3 (11.0)
Epilepsy duration, mean (SD), y[d]	21.6 (12.5)	16.6 (10.0)
Seizure frequency/28 days, median (range)	9.2 (0-17.304)[e]	5.7 (2-27)[f]
Epileptic seizure types experienced during baseline of the previous trial, n (%)[g,h]		
Focal (partial-onset) seizures	647 (99.8)[i]	0
Focal aware (simple partial)	190 (29.3)	0
Focal impaired awareness (complex partial)	513 (79.2)	0
Focal to bilateral tonic-clonic (partial evolving to secondary generalized)	234 (36.1)	0
Generalized seizures	14 (2.2)	15 (100)
Absence	2 (0.3)	4 (26.7)
Myoclonic	0	3 (20.0)
Clonic	1 (0.2)	0
Tonic	3 (0.5)	0
Tonic-clonic	3 (0.5)	9 (60.0)
Atonic	2 (0.3)	0
Number of previous AEDs, n (%)[j]		
0-1	294 (45.4)	7 (46.7)
2-4	281 (43.4)	7 (46.7)
≥5	73 (11.3)	1 (6.7)
Number of concomitant AEDs, n (%)[k]		
1	127 (19.6)	4 (26.7)
2	443 (68.4)	8 (53.3)
3	78 (12.0)	3 (20.0)
Concomitant AEDs taken by ≥10% of patients in either group[l,m]		
Carbamazepine	312 (48.1)	6 (40.0)
Phenytoin[n]	176 (27.2)	3 (20.0)
Clobazam	171 (26.4)	7 (46.7)
Lamotrigine	167 (25.8)	2 (13.3)
Levetiracetam	120 (18.5)	3 (20.0)
Topiramate	110 (17.0)	2 (13.3)
Oxcarbazepine	96 (14.8)	3 (20.0)
Phenobarbital	68 (10.5)	2 (13.3)

(continues)

TABLE 1 (Continued)

	Focal seizure, ES, n = 648	PGS, ES, n = 15
Valproate[o]	168 (25.9)	6 (40.0)
Garoin	0	2 (13.3)

Abbreviations: AEDs, antiepileptic drugs; ES, efficacy set; PGS, primary generalized seizure; SD, standard deviation; SS, safety set.

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

[c]n = 649.

[d]Relative to date of first seizure.

[e]Data represent seizures/28 days.

[f]Data represent seizure days/28 days.

[g]Patients may have had more than one type of seizure.

[h]Seizure types are listed per the International League Against Epilepsy (ILAE) 2017[26] classification, with the old terminology (ILAE 1981) in parentheses.[27]

[i]One patient was consented to the trial but never received brivaracetam; this patient was discontinued due to loss to follow-up.

[j]Taken within 5 years and discontinued before entry into the previous trial.

[k]At entry into the previous trials.

[l]World Health Organization Drug Reference List (June 2012 version) preferred drug name.

[m]At any time during the trial.

[n]Includes phenytoin, phenytoin sodium, fosphenytoin, and fosphenytoin sodium;

[o]Includes valproate sodium, valproate semisodium, valproic acid, and valproate magnesium.

drug-related by the investigator (reported by ≥5% of patients overall) were dizziness (82 [12.3%] patients), somnolence (61 [9.1%] patients), headache (52 [7.8%] patients), and depression (37 [5.5%] patients). Fifty-three (7.9%) patients discontinued brivaracetam due to drug-related TEAEs, the most common of which (reported by

TABLE 2 Incidence of TEAEs (safety set)

	Overall, N = 667, n (%)	Focal seizure, N = 652, n (%)	PGS, N = 15, n (%)
Any TEAE	608 (91.2)	595 (91.3)	13 (86.7)
Drug-related TEAEs[a]	378 (56.7)	371 (56.9)	7 (46.7)
Serious TEAEs	152 (22.8)	149 (22.9)	3 (20.0)
Drug-related serious TEAEs[a]	30 (4.5)	28 (4.3)	2 (13.3)
Severe TEAEs	182 (27.3)	180 (27.6)	2 (13.3)
Permanent discontinuation of brivaracetam due to TEAEs	99 (14.8)	96 (14.7)	3 (20.0)
Deaths	18 (2.7)	18 (2.8)	0
TEAEs reported by ≥10% of patients overall, MedDRA version 15.0 preferred term			
Headache	166 (24.9)	165 (25.3)	1 (6.7)
Dizziness	143 (21.4)	143 (21.9)	0
Nasopharyngitis	94 (14.1)	92 (14.1)	2 (13.3)
Somnolence	91 (13.6)	88 (13.5)	3 (20.0)
Influenza	84 (12.6)	84 (12.9)	0
Convulsion[b]	82 (12.3)	81 (12.4)	1 (6.7)
Upper respiratory tract infection	76 (11.4)	75 (11.5)	1 (6.7)
Depression	71 (10.6)	70 (10.7)	1 (6.7)
Pyrexia	69 (10.3)	65 (10.0)	4 (26.7)
Nausea	67 (10.0)	67 (10.3)	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PGS, primary generalized seizures; TEAE, treatment-emergent adverse event.

[a]The relationship was assessed by the investigator.

[b]Convulsions were reported as TEAEs if their nature changed considerably or their frequency or intensity increased as compared to the clinical profile known to the investigator from the patient's history or baseline period.

at least four patients overall) were depression (five [0.7%] patients), suicidal ideation (five [0.7%] patients), and dizziness (four [0.6%] patients).

3.2.4 | Serious TEAEs

A total of 152 (22.8%) patients reported at least one serious TEAE (Table 2; SS). The serious TEAEs experienced by ≥1% of patients overall were convulsion (15 patients [2.2%]), pneumonia (seven patients [1.0%]), and suicide attempt (seven patients [1.0%]). Eighteen deaths (2.7% of patients) were reported, two of which were considered treatment-related; one completed suicide and one sudden unexplained death in epilepsy were considered by the investigator as possibly related to brivaracetam; all other fatal events were assessed as unlikely or not related.

3.2.5 | Other safety outcomes

No clinically relevant findings were observed for any mean changes from baseline in hematology, blood chemistry, urinalysis parameters, vital signs, body weight, or ECGs.

Columbia–Suicide Severity Rating Scale

A total of 51 (7.6%; SS) patients had a positive response on the C-SSRS at any time during the trial. Seven patients (1.0%) had a serious TEAE of suicide attempt; four of these TEAEs were assessed as drug-related by the investigator. Two patients (0.3%) completed suicide. Sixteen patients (2.4%) had TEAEs of suicidal ideation; eight of these TEAEs were assessed by the trial investigator as drug-related.

Hospital Anxiety and Depression Scale

Mean anxiety and depression scores indicated normal to mild levels of anxiety and depression at baseline (Table 3; SS). At last value, the mean changes from baseline in anxiety and depression scores were −0.7 (standard deviation [SD] = 4.3) and −0.2 (SD = 4.4), respectively. Changes from baseline over time for anxiety were all negative, indicating improvement. Depression score showed minor decreases from baseline over time.

3.3 | Efficacy and quality of life outcomes

3.3.1 | Focal seizure frequency

The median focal seizure frequency per 28 days for patients with focal seizures decreased from 9.2 (range = 0-17.304) at the previous trial baseline to 4.2 (range = 0-11.726) during the evaluation period (focal seizure ES). The median reduction

TABLE 3 Hospital Anxiety and Depression Scale scores (safety set)

Trial visit cohort,[a] time point	Observed values, mean (SD)	Change from baseline, mean (SD)
Anxiety score		
2-mo cohort, n = 378		
Baseline	8.0 (4.0)	
Month 2	7.1 (3.9)	−0.9 (4.0)
6-mo cohort, n = 328		
Baseline	8.0 (4.0)	
Month 6	6.8 (3.9)	−1.1 (4.3)
12-mo cohort, n = 290		
Baseline	8.0 (4.1)	
Month 12	7.0 (4.2)	−1.0 (4.2)
18-mo cohort, n = 260		
Baseline	8.1 (4.2)	
Month 18	6.9 (4.0)	−1.2 (4.0)
24-mo cohort, n = 234		
Baseline	8.1 (4.1)	
Month 24	6.8 (3.9)	−1.3 (4.3)
Last value, n = 397		
Baseline	8.0 (4.0)	
Outcome	7.4 (4.1)	−0.7 (4.3)
Depression score		
2-mo cohort, n = 377		
Baseline	6.1 (4.0)	
Month 2	5.4 (3.9)	−0.7 (3.9)
6-mo cohort, n = 328		
Baseline	6.0 (4.0)	
Month 6	5.4 (3.9)	−0.6 (4.3)
12-mo cohort, n = 289		
Baseline	6.1 (4.1)	
Month 12	5.4 (3.9)	−0.6 (4.2)
18-mo cohort, n = 260		
Baseline	6.0 (4.1)	
Month 18	5.7 (4.0)	−0.4 (4.1)
24-mo cohort, n = 234		
Baseline	6.1 (4.0)	
Month 24	5.5 (3.9)	−0.6 (4.4)
Last value, n = 396		
Baseline	6.1 (4.0)	
Outcome	5.9 (4.2)	−0.2 (4.4)

Abbreviation: SD, standard deviation.

[a]Trial visit cohorts define groups of patients who have completed the scheduled visit at the time point defined by the cohort (eg, the 24-month cohort includes patients who completed the scheduled visit at the end of year 2).

from baseline in focal seizure frequency per 28 days was 57.3% overall and increased with each exposure duration cohort through the 36-month cohort, and then remained stable through the 108-month cohort (Table 4). Overall, the 50% responder rate was 55.6% (360/648 patients); the rate increased by exposure duration cohort through the 36-month cohort and remained generally consistent through the 108-month cohort (Figure 1).

During the evaluation period, 170 (30.3%) patients with focal seizures were continuously seizure-free (for all seizure types) for at least 6 months and 114 (20.3%) were seizure-free for at least 12 months (Figure 2). Rates of 6-month and 12-month seizure freedom generally increased with each exposure duration cohort through to the 84-month cohort and then stabilized. Of 16 patients in the 132-month cohort, four patients were seizure-free for 6 years, three patients were seizure-free for 8 years, and one patient was seizure-free for 10 years. Seizure frequency assessments were also completed for patients with PGS, but because of the small number of patients (n = 12-15; PGS ES) meaningful interpretations could not be made.

3.3.2 | EuroQol-5 dimensions questionnaire

No substantial change in the EQ-5D health status item was observed during the trial in the overall trial population (Table S3; ES).

3.3.3 | Patient-weighted Quality of Life in Epilepsy Inventory

In a post hoc analysis of the ES, the total QOLIE-31-P score showed a mean (SD) improvement from baseline of 5.7 (16.1) at month 12 and 6.5 (18.0) at month 24 (Table S4), which are approximately equivalent to effect sizes (Cohen's *d*) of 0.35 and 0.36, respectively.

TABLE 4 Percentage reduction in focal seizure frequency from baseline (focal seizure efficacy set)

Efficacy time interval	n	Mean (SD)	Median (Q1, Q3)
On treatment	647	38.2 (94.3)	57.3 (18.6, 82.2)
Months 1-12	485	47.3 (57.9)	57.3 (30.8, 81.6)
Months 1-24	411	54.2 (45.7)	62.7 (37.8, 85.5)
Months 1-36	353	59.0 (39.4)	67.1 (42.5, 88.4)
Months 1-48	318	60.3 (40.0)	69.1 (44.6, 89.5)
Months 1-60	274	59.4 (42.0)	69.0 (43.1, 87.5)
Months 1-72	243	59.9 (42.5)	70.0 (43.5, 87.8)
Months 1-84	219	61.4 (42.5)	70.8 (47.3, 91.0)
Months 1-96	173	62.0 (44.0)	71.1 (51.5, 91.4)
Months 1-108	83	67.0 (33.2)	74.3 (51.7, 94.4)

Note: Exposure duration cohorts define groups of patients with at least the specified duration of exposure. Baseline values were calculated from the seizure diary data collected during the baseline period of the previous trial.

Abbreviation: SD, standard deviation.

4 | DISCUSSION

In this up to 11-year, open-label, multinational, follow-up trial of adjunctive brivaracetam at individualized doses up to 200 mg/d in adult patients with focal seizures (with or without secondary generalization) or PGS, the duration of patients' participation depended on several factors. Over time, patients left the trial when brivaracetam became commercially available or when they transitioned to a managed access program. Therefore, the timing of commercial availability of brivaracetam in each country may have affected the overall duration of exposure for this trial. Furthermore, some patients discontinued the trial due to TEAEs or lack of efficacy. Therefore, results should be interpreted with the knowledge that patients who responded well to brivaracetam were more likely to remain in the trial for longer. Approximately half of the patients were still in the trial at 4 years, and 12.4% remained in the trial at 9 years. The duration of exposure in this trial is long even among long-term follow-up trials of AEDs.[13-18]

During extended treatment, brivaracetam was generally safe and well tolerated, with only a small proportion of patients permanently discontinuing brivaracetam due to TEAEs. This could be related to the flexible-dose trial design, which allowed dose adjustment of brivaracetam and concomitant AEDs, as well as addition and discontinuation of concomitant AEDs to optimize tolerability. The most common TEAEs in patients with focal seizures were headache and dizziness, consistent with other brivaracetam trials.[5-9,19-21] Overall, the incidence of TEAEs was slightly higher in the first 3 months of treatment than in the following time intervals. This is not unexpected, as patients who received placebo in the previous trials received brivaracetam for the first time in this trial, and patients who may have been on a lower dose of brivaracetam in the previous trials received an up-titration when they transitioned to this long-term follow-up trial.

The median reduction in focal seizure frequency (57.3%) and 50% responder rate (55.6%) observed in this trial are similar to those reported for a pooled analysis of data from phase 2b, phase 3, and long-term follow-up trials of adjunctive brivaracetam in adults with uncontrolled focal seizures, which included the current trial among the nine trials in the efficacy analysis.[5] In that pooled analysis, the median reduction in focal seizure frequency was approximately 50% and the 50% responder rate was 48.9% for patients who received modal brivaracetam doses of 5-200 mg/d. The current results are also consistent with

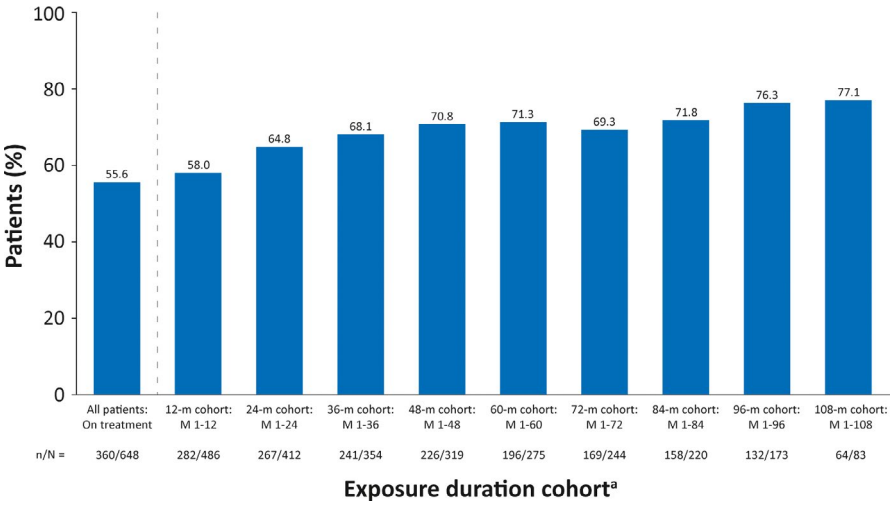

FIGURE 1 Fifty percent responder rate for focal seizure frequency from baseline of previous trial (focal seizure efficacy set). M, months; m, month; n, number of patients who achieved at least a 50% reduction in focal seizure frequency from baseline; N, total number of patients assessed in each exposure duration cohort. [a]Percentages for the overall summary for each exposure duration cohort were relative to the number of patients included in the cohort; exposure duration cohorts defined groups of patients with at least the specified duration of exposure

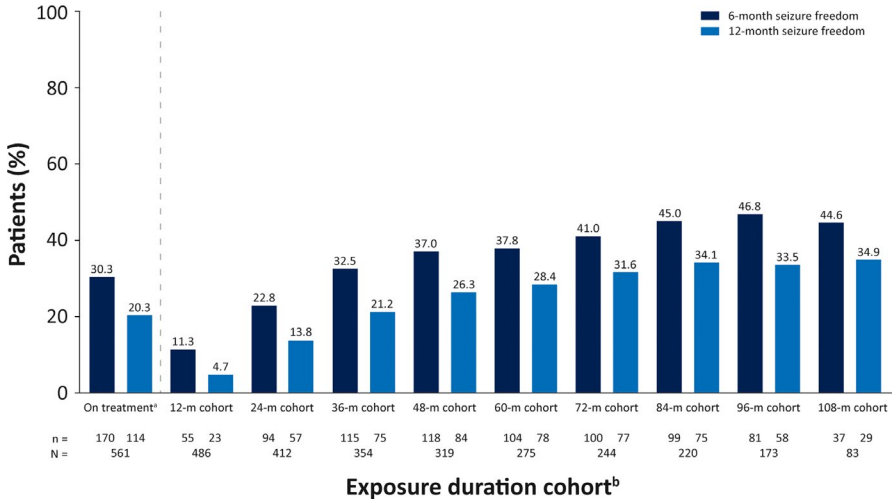

FIGURE 2 Continuous seizure freedom for ≥6 months and ≥12 months at any time during brivaracetam treatment in patients with focal seizures (focal seizure efficacy set). Percentages are relative to the number of patients within each exposure duration cohort. Patients had to have seizure diary entries 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 failed for seizure freedom. [a]n = number of patients who reported no seizures with brivaracetam for at least 6 and 12 months at any time during treatment. [b]n = number of patients who reported no seizures with brivaracetam for at least 6 and 12 months at any time during the cohort interval. m, month; N, total number of patients assessed in each exposure duration cohort

those reported in long-term follow-up trials of other AEDs in patients with focal seizures (overall data: median reduction in seizure frequency of 32%-53%, 50% responder rate of 37%-53%).[13,15,17] As reported for the pooled analysis,[5] with increasing exposure duration, patients with focal seizures experienced greater improvements in focal seizure frequency and continuous seizure freedom. This could potentially be explained by changes to concomitant AED treatments and optimization of brivaracetam doses in this long-term extension trial. Although patients who responded well to brivaracetam were more likely to remain in the trial, the data show that efficacy was maintained for those patients who continued treatment.

The EQ-5D health status item showed no substantial change in the overall population during the trial. These are the first EQ-5D visual analog scale data reported for brivaracetam. The minor changes were as expected, because EQ-5D is not sensitive in treatment-resistant epilepsy, as previously shown by an analysis of data from phase 3 trials of adjunctive brivaracetam in patients with uncontrolled focal seizures.[22] A study that compared different generic preference-based health-related quality of life instruments in adults evaluated

for epilepsy surgery also showed that EQ-5D was relatively insensitive to seizure control at 2 years.[23]

In the overall trial population, QOLIE-31-P total score showed mean improvements at month 12 and at month 24 that are close to a "moderate improvement" in general convention. Additional post hoc analyses of the ES showed that at 12 months, 49% of patients had a clinically meaningful improvement in QOLIE-31-P total score, defined as a change larger than a previously defined minimally important change (MIC) threshold,[24] whereas 23% of patients showed a worsening (lower than the negative MIC); at 24 months, 52% of patients had a clinically meaningful improvement and 21% worsened (data not shown).

These results are consistent with the pooled dataset.[5] The mean change in QOLIE-31-P total score was similar to that seen in the pooled dataset at month 24 in patients who received modal brivaracetam doses of 5-200 mg/d (6.5 vs approximately 5.5)[5]; however, a greater mean change was observed in the current trial for the subscores of emotional well-being (3.9 vs approximately 2.5), energy/fatigue (6.2 vs approximately 3.5), medication effects (5.2 vs approximately 3.5), and overall quality of life (7.0 vs approximately 5), and a lower mean change was observed for seizure worry (11.3 vs approximately 13). Geographic differences could have influenced the results; the current trial was conducted in Australia, Brazil, Canada, India, Mexico, and the USA and excluded Europe, whereas the pooled analysis included trials conducted in Africa, the Asia-Pacific, Europe, North America, and South America. The mean change in QOLIE-31-P scores was also higher than in short-term double-blind data,[25] highlighting the need for longer-term follow-up to assess treatment effects on quality of life.

The HADS data presented in this report are the first for brivaracetam. Baseline anxiety and depression scores indicated normal to mild levels of anxiety and depression. In all trial visit cohorts, the anxiety score showed a numerical improvement from baseline. The depression score remained unchanged at the last value.

Limitations of this trial include the open-label, single-arm design and the small number of patients with PGS enrolled, which does not allow meaningful conclusions to be drawn for those patients. Although the flexible-dose trial design limits the conclusions that can be drawn regarding the relationship between brivaracetam dose and efficacy, individualized dosing is closer to clinical practice than fixed dosing.

5 | CONCLUSION

In this long-term follow-up trial, adjunctive brivaracetam therapy was well tolerated, with a good safety profile in adults with epilepsy at individualized doses up to 200 mg/d. The safety profile of brivaracetam is consistent with that in previous studies. Approximately half of the patients remained in the trial at 4 years. Brivaracetam resulted in reductions in focal seizure frequency. Efficacy outcomes improved with increasing duration of brivaracetam exposure, with changes remaining stable through the 9-year cohort. These findings support the long-term use of adjunctive brivaracetam to treat patients with focal seizures.

ACKNOWLEDGMENTS

This trial was funded by UCB Pharma. The authors thank the patients and their caregivers, in addition to the investigators (listed in Appendix S1) and their teams who contributed to this trial. The authors acknowledge Barbara Pelgrims, PhD (UCB Pharma, Brussels, Belgium) for reviewing the manuscript and overseeing publication development. Writing assistance was provided by Emily Chu, PhD (Evidence Scientific Solutions, London, UK), and was funded by UCB Pharma.

CONFLICT OF INTEREST

T.J.O. has received support from and/or has served as a paid consultant for Eisai Pharmaceuticals, National Health and Medical Research Council, National Institute of Neurological Disorders and Stroke, Praxis Precision Medicines, Royal Melbourne Hospital Neuroscience Foundation, UCB Pharma, and Zynerba Pharmaceuticals. S.B., A.-L.S., and S.Y. are employees of UCB Pharma. S.B. has received UCB Pharma stocks from his employment. Q.H. was an employee of UCB Pharma at the time when the trial was conducted. V.B. has no conflicts of interest to report. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA ACCESSIBILITY STATEMENT

Underlying data from this article may be requested by qualified researchers 6 months after product or indication approval in the USA and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient data and redacted study documents, which may include raw datasets, analysis-ready datasets, study protocol, blank case report form, 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.clinicalstudydatarequest.com and a signed data-sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal.

ORCID

Terence J. O'Brien https://orcid.org/0000-0002-7198-8621

REFERENCES

1. UCB Inc, Smyrna, GA, USA. Briviact® (brivaracetam) Prescribing Information. 2018. Available at: https://www.briviact.com/briviact-PI.pdf. Accessed March 16, 2020.
2. UCB Pharma SA, Brussels, Belgium. Briviact® (brivaracetam). Summary of product characteristics. 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/briviact-epar-product-information_en.pdf. Accessed March 16, 2020.
3. UCB Pharma, Malvern, Australia. Briviact® (brivaracetam) film-coated tablets and oral solution. 2019. Available at: https://ucbaustralia.com.au/_up/ucbaustralia_com_au/documents/Briviact_PI_Oral.pdf. Accessed March 16, 2020.
4. UCB Pharma, Malvern, Australia. Briviact® (brivaracetam) solution for injection. 2019. Available at: https://ucbaustralia.com.au/_up/ucbaustralia_com_au/documents/Briviact_PI_IV.pdf. Accessed March 16, 2020.
5. Toledo M, Whitesides J, Schiemann J, et al. Safety, tolerability, and seizure control during long-term treatment with adjunctive brivaracetam for partial-onset seizures. Epilepsia. 2016;57:1139–51.
6. French JA, Costantini C, Brodsky A, von Rosenstiel P; N01193 Study Group. Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. Neurology. 2010;75:519–25.
7. Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia. 2014;55:47–56.
8. Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia. 2014;55:57–66.
9. Kwan P, Trinka E, Van Paesschen W, Rektor I, Johnson ME, Lu S. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. Epilepsia. 2014;55:38–46.
10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67:361–70.
11. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168:1266–77.
12. Cramer JA, Perrine K, Devinsky O, Bryant-Comstock L, Meador K, Hermann B. Development and cross-cultural translations of a 31-item quality of life in epilepsy inventory. Epilepsia. 1998;39:81–8.
13. Gil-Nagel A, Brodie MJ, Leroy R, et al. Safety and efficacy of ezogabine (retigabine) in adults with refractory partial-onset seizures: interim results from two ongoing open-label studies. Epilepsy Res. 2012;102:117–21.
14. Halász P, Cramer JA, Hodoba D, et al. Long-term efficacy and safety of eslicarbazepine acetate: results of a 1-year open-label extension study in partial-onset seizures in adults with epilepsy. Epilepsia. 2010;51:1963–9.
15. Rektor I, Krauss GL, Bar M, et al. Perampanel study 207: long-term open-label evaluation in patients with epilepsy. Acta Neurol Scand. 2012;126:263–9.
16. Krauss GL, Perucca E, Ben-Menachem E, et al. Long-term safety of perampanel and seizure outcomes in refractory partial-onset seizures and secondarily generalized seizures: results from phase III extension study 307. Epilepsia. 2014;55:1058–68.
17. Hufnagel A, Ben-Menachem E, Gabbai AA, Falcão A, Almeida L, Soares-da-Silva P. Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: results of a 1-year open-label extension study. Epilepsy Res. 2013;103:262–9.
18. Toledo M, Beale R, Evans JS, et al. Long-term retention rates for antiepileptic drugs: a review of long-term extension studies and comparison with brivaracetam. Epilepsy Res. 2017;138:53–61.
19. Klein P, Schiemann J, Sperling MR, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia. 2015;56:1890–8.
20. Yates SL, Fakhoury T, Liang W, Eckhardt K, Borghs S, D'Souza J. An open-label, prospective, exploratory study of patients with epilepsy switching from levetiracetam to brivaracetam. Epilepsy Behav. 2015;52:165–8.
21. Van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. Epilepsia. 2013;54:89–97.
22. Mukuria C, Young T, Keetharuth A, Borghs S, Brazier J. Sensitivity and responsiveness of the EQ-5D-3L in patients with uncontrolled focal seizures: an analysis of phase III trials of adjunctive brivaracetam. Qual Life Res. 2017;26:749–59.
23. Langfitt JT, Vickrey BG, McDermott MP, et al. Validity and responsiveness of generic preference-based HRQOL instruments in chronic epilepsy. Qual Life Res. 2006;15:899–914.
24. Borghs S, de la Loge C, Cramer JA. Defining minimally important change in QOLIE-31 scores: estimates from three placebo-controlled lacosamide trials in patients with partial-onset seizures. Epilepsy Behav. 2012;23:230–4.
25. Brandt C, Borghs S, Elmoufti S, Mueller K, Townsend R, de la Loge C. Health-related quality of life in double-blind phase III studies of brivaracetam as adjunctive therapy of focal seizures: a pooled, post-hoc analysis. Epilepsy Behav. 2017;69:80–5.
26. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522–30.
27. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia. 1981;22:489–501.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: O'Brien TJ, Borghs S, He Q, Schulz A-L, Yates S, Biton V. Long-term safety, efficacy, and quality of life outcomes with adjunctive brivaracetam treatment at individualized doses in patients with epilepsy: An up to 11-year, open-label, follow-up trial. *Epilepsia*. 2020;61:636–646. https://doi.org/10.1111/epi.16484