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Long-term efficacy and tolerability of adjunctive brivaracetam in adults with focal to bilateral tonic-clonic (secondary generalized) seizures: Post hoc pooled analysis

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ABSTRACT

This post hoc analysis was conducted to evaluate the efficacy, tolerability, and health-related quality of life during long-term adjunctive brivaracetam (BRV) treatment in adult patients with focal to bilateral tonic-clonic seizures (FBTCS). Patients (≥ 16 years) were included in this post hoc analysis if they were randomized to BRV or placebo in double-blind, placebo-controlled (N01252 [NCT00490035], N01253 [NCT00464269], N01358 [NCT01261325]; core) trials, and received adjunctive BRV in the corresponding long-term follow-up (N01125 [NCT00175916], N01199 [NCT00150800], N01379 [NCT01339559]) trials, and reported FBTCS during the 8-week prospective baseline (core trial). Efficacy (concomitant levetiracetam excluded) and tolerability (concomitant levetiracetam included) were assessed from the first day of BRV in patients who initiated BRV at 50–200 mg/day.

Two hundred and eighty-four patients reported FBTCS during baseline (core trials) and were included in the Efficacy Set. Patients (mean age of 37.0 years; 51.8% male; mean epilepsy duration of 22.4 years; median baseline frequency of 2.8 FBTCS per 28 days) received BRV for a median treatment duration of 2.5 years (range< 0.1–11.3) at a median modal dose of 150 mg/day. BRV was discontinued by 175 (61.6%) patients, most commonly (≥ 10% of patients) due to adverse event (18.3%), lack of efficacy (18.3%), and consent withdrawn (11.6%); the median time to discontinuation of BRV due to any reason was 358.5 days. The Kaplan-Meier (KM)-estimated retention on BRV at 1, 3, and 5 years, were 69.3%, 48.2%, and 37.3%, respectively. The KM-estimated proportion of patients not discontinuing BRV due to lack of efficacy or adverse event were 80.0%, 63.9%, and 57.2% at 1, 3, and 5 years, respectively. Overall, the median percentage reduction in FBTCS frequency from baseline was 76.2%, and the 50% and 75% responder rates for FBTCS were 68.7% and 50.7%, respectively, which were sustained over time across completer cohorts. Sustained 50%, 75%, and 100% response in FBTCS from day 1 of adjunctive BRV treatment during the entire first year was estimated for 32.5%, 21.1%, and 15.0% of patients, respectively (KM analysis), and showed maintenance or improvement in the response to BRV over time. For patients with ≥ 1 year of BRV exposure, 51.3% were free from FBTCS for ≥ 1 year during any time of the treatment period, and 22.8% of patients did not report FBTCS during the first year from the first day of treatment. Clinically meaningful improvements in total Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) score were reported by 43.6% and 46.4% of patients after 1 and 2 years of treatment, respectively. The largest improvements in the QOLIE-31-P score, with > 50% of patients reporting a clinically meaningful improvement, were observed in the seizure worry and daily activities/social functioning subscales after 1 and 2 years of BRV treatment. Overall, 278/313 (88.8%; Safety Set) patients reported at least one

Abbreviations: AE, adverse event; ASM, antiseizure medication; BRV, brivaracetam; CI, confidence interval; ES, Efficacy Set; FBTCS, focal to bilateral tonic-clonic seizures; HRQoL, health-related quality of life; KM, Kaplan-Meier; QOLIE-31-P, Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; SD, standard deviation; SS, Safety Set; SUDEP, sudden unexpected death in epilepsy; SV2A, synaptic vesicle protein 2A; TEAE, treatment-emergent adverse event.

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treatment-emergent adverse event (TEAE), 170 (54.3%) had a drug-related TEAE, 88 (28.1%) had a serious TEAE, and 55 (17.6%) discontinued BRV due to a TEAE.

Overall, long-term adjunctive BRV was generally well tolerated and reduced the frequency of FBTCS in adults, with 22.8% of patients (who completed ≥ 1 year of treatment) not reporting any FBTCS during the first year from the first day of BRV treatment.

1. Introduction

Brivaracetam (BRV) is an antiseizure medication (ASM) with high and selective affinity for synaptic vesicle protein 2A (SV2A) in the brain, with a 15- to 30-fold higher affinity than levetiracetam (Gillard et al., 2011; Matagne et al., 2008). BRV is indicated as monotherapy (in the United States) and as adjunctive treatment (in the United States and European Union) of focal seizures with or without focal to bilateral tonic-clonic seizures (FBTCS; secondary generalized seizures) in patients 4 years of age and older (UCB Inc, 2018; UCB Pharma, 2020). BRV is also approved in multiple other regions globally, including several countries across the Asia Pacific region and North and South America.

Patients with tonic-clonic seizures have a greater risk of injury and falls (Lawn et al., 2004), higher mortality (Lhatoo et al., 2001), higher risk of sudden unexpected death in epilepsy (SUDEP) (Devinsky, 2011; Hirsch et al., 2011; Laxer et al., 2014; Shorvon and Tomson, 2011), and worse quality of life (Viteva, 2014), compared to patients with other seizure types. Tonic-clonic seizure frequency has been reported as the most important risk factor for SUDEP (Shorvon and Tomson, 2011). Importantly, in patients with drug-resistant seizures, reducing tonic-clonic seizure frequency to two or fewer seizures per year after epilepsy surgery has been associated with a significant reduction in mortality, comparable with that for patients who are entirely seizure free (Sperling et al., 2016). Therefore, it is important to reduce the frequency and burden of FBTCS, in order to reduce morbidity and mortality of people with epilepsy, and improve their quality of life.

Previous post hoc analyses of pooled data from three double-blind, placebo-controlled, fixed-dose Phase III trials showed that adjunctive BRV 50–200 mg/day reduced the frequency of FBTCS over 12 weeks in patients with FBTCS at baseline, with higher level of response generally observed with higher BRV doses (Moseley et al., 2016). The majority of patients with FBTCS who achieved 75–100% sustained seizure frequency reduction with oral BRV (100 or 200 mg/day) achieved this response from the first day of BRV treatment (Klein et al., 2020a).

The aim of this analysis was to evaluate the long-term efficacy, tolerability, and health-related quality of life (HRQoL) of adjunctive BRV in adult patients with FBTCS, by exploring pooled data from the three aforementioned double-blind Phase III trials of adjunctive BRV and the corresponding open-label, long-term follow-up trials.

2. Methods

2.1. Trials and populations

In the core, 12-week, fixed-dose, Phase III trials (N01252 [NCT00490035] (Ryvlin et al., 2014), N01253 [NCT00464269] (Biton et al., 2014), N01358 [NCT01261325] (Klein et al., 2015)), adult patients (≥ 16 years) with focal seizures were randomized to placebo or BRV 5, 20, 50, 100, or 200 mg/day, in addition to one or two other ASMs. Patients who subsequently entered a corresponding long-term follow-up trial (N01125 [NCT00175916] (Ben-Menachem et al., 2021), N01199 [NCT00150800] (O'Brien et al., 2020), N01379 [NCT01339559] (Toledo et al., 2021)) were allowed to receive BRV up to 200 mg/day. The treatment duration in the long-term follow-up trials ranged from up to 8 years in N01379 to up to 14 years in N01125.

Post hoc efficacy, tolerability, and HRQoL analyses were completed using data from patients who received placebo or BRV in each core trial, had FBTCS during the 8-week prospective baseline of the core trial (whether or not they had other types of seizures), and initiated BRV at a dose 50–200 mg/day (the approved therapeutic dose range for adults) during either the core or long-term follow-up trial. Data for patients who received BRV during a double-blind trial and did not enroll in a long-term follow-up trial were included in the analysis. Efficacy and tolerability were assessed from the first day of BRV treatment in patients randomized to BRV in the core trial, and from the first day in the long-term follow-up trial in patients randomized to placebo in the core trial (the last visit of the core trial was classified as the start of the long-term follow-up trial).

2.2. Outcomes and statistical analysis

Efficacy outcomes were assessed in patients randomized to BRV or placebo (core trial) who had at least one post-baseline seizure diary entry during adjunctive BRV treatment, excluding those taking concomitant levetiracetam during the core or long-term follow-up trials (Efficacy Set; ES). Efficacy data were also analyzed in completer cohorts comprising patients who received BRV and had seizure diary data for the specified duration across the core and long-term follow-up trials combined. For example, patients completing at least 1 year of BRV treatment were included in the 1-year completer cohort, with 1 year defined as 52 weeks or 364 days. The frequency of FBTCS was standardized to 28 days.

Efficacy outcomes included percentage reduction from baseline (core trials) in FBTCS frequency per 28 days, and 50% and 75% responder rates (patients with a ≥ 50% or ≥ 75% reduction in FBTCS frequency from baseline, respectively), analyzed for the overall population and by BRV modal dose, yearly completer cohorts, number of prior ASMs (discontinued before BRV initiation), number of concomitant ASMs at BRV initiation, age at epilepsy onset, and epilepsy duration; time to 50%, 75%, and 100% sustained response in FBTCS during the first year of BRV treatment (overall and by BRV modal dose category); freedom from FBTCS by yearly completer cohort; and the proportion of patients reporting none, or one to two FBTCS by yearly completer cohort and time interval. The number of days with FBTCS per patient per 8 weeks during the 8-week baseline and by 8-week intervals during BRV treatment were also analyzed for the overall population, by 50% responder status, and by yearly completer cohorts. The time from baseline start to the first FBTCS during baseline, the time from the last FBTCS before BRV initiation to BRV initiation, and the time from BRV initiation to the first FBTCS were also assessed.

The probability of patients who achieved sustained responder status during the first year of BRV treatment was estimated by the Kaplan-Meier (KM) method. Patients were classified as sustained 50%, 75%, or 100% responders on a particular day if they completed the entire period through day 364 and were a ≥ 50%, ≥ 75%, or 100% responder (based on percentage reduction in FBTCS frequency from baseline) both on that day and for every successive day through day 364. Patients who discontinued treatment before day 364 were classified as non-responders; by definition, these patients never achieved a sustained responder status.

For assessments of continuous freedom from FBTCS, patients were defined as FBTCS-free if they had a period of consecutive days with no FBTCS for at least 1, 2, 3, 4, or 5 years at any time during BRV treatment, and the seizure diary was completed for at least 90% of days within the specified BRV treatment interval. Assessment of the proportion of patients not reporting FBTCS or reporting one to two FBTCS per year of BRV treatment was also assessed in the yearly completer cohorts.

Tolerability outcomes were assessed in patients who initiated BRV at 50–200 mg/day, including patients taking concomitant levetiracetam (Safety Set; SS). Tolerability outcomes included treatment-emergent adverse events (TEAEs), TEAEs considered drug-related, severe TEAEs, serious TEAEs, discontinuations due to adverse events (AEs), psychiatric TEAEs, TEAEs potentially associated with behavioral disorders, and deaths. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0 (www.meddra.org, March 2012). Signs or symptoms of epilepsy were recorded as TEAEs only if their nature changed considerably or their frequency or intensity increased in a clinically significant manner as compared to the clinical profile known to the investigator from the patient's history or baseline period. Reported TEAEs were not considered as adverse drug reactions, and as such not attributed to BRV by default. Therefore, seizure worsening episodes would not be automatically considered BRV related. Psychiatric TEAEs were classified using the MedDRA System Organ Class "Psychiatric disorders". TEAEs associated with behavioral disorders were based on the medical review of the MedDRA dictionary of Preferred Terms. The Preferred Terms associated with behavioral disorders reported by more than one patient included irritability, aggression, abnormal behavior, agitation, and anger.

The change from baseline, and proportion of patients with a clinically meaningful improvement from baseline, in Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) total score and subscale scores (Cramer et al., 2003) after 1 and 2 years of adjunctive BRV treatment were assessed in the ES. QOLIE-31-P is a patient-reported epilepsy-specific HRQoL instrument (scored 0–100; higher scores represent better functioning). A clinically meaningful improvement in QOLIE-31-P was defined as a change from baseline of greater than 5.19 points for the total score, and for the subscale scores, a change from baseline of greater than 7.42 for seizure worry, 3.95 for daily activities/social function, 5.25 for energy/fatigue, 4.76 for emotional well-being, 5.34 for cognitive function, 5.00 for medication effects, and 6.42 for overall quality of life (Borghs et al., 2012). For patients taking BRV during the core trial, the QOLIE-31-P time points were 1 and 2 years plus 84 days.

An analysis was conducted to determine the time from BRV initiation to first FBTCS or first TEAE of grand mal convulsion during BRV treatment in patients with no history of FBTCS.

Due to the post hoc nature of this analysis, and the observational nature of the long-term follow-up trials, no formal statistical testing was conducted. The time to discontinuation due to any reason, lack of efficacy, AEs, or lack of efficacy or AEs, and the time to sustained response during the first year of BRV treatment were estimated by the KM method.

3. Results

3.1. Baseline characteristics

Overall, a total of 313 patients reported FBTCS during baseline and initiated BRV at 50–200 mg/day and were included in the SS, including a small number of patients ($n = 29$) taking concomitant levetiracetam. In the ES (which excluded patients taking concomitant levetiracetam), 284 patients reported FBTCS during baseline and initiated BRV 50–200 mg/day. At baseline, patients in the ES had a mean (standard deviation [SD]) age of 37.0 (12.5) years and a mean (SD) epilepsy duration of 22.4 (12.8) years; 51.8% were male (Table 1).

In the overall ES, the median baseline FBTCS frequency was 2.8 seizures per 28 days. Patients in the BRV $\leq$ 100 mg/day modal dose group had a higher median baseline FBTCS frequency (3.5/28 days) compared with patients on higher BRV modal doses ($>$ 100 to $<$ 200 mg/day: 3.0/28 days; 200 mg/day: 2.0/28 days).

At BRV initiation, patients were taking a mean (SD) of approximately two (0.5) concomitant ASMs. A slightly higher proportion of the BRV 200 mg/day modal dose group had only one concomitant ASM compared with the other groups. Of the 284 patients (ES) with baseline FBTCS, 253 (89.1%) entered one of the long-term follow-up trials of BRV.

3.2. BRV dosing, treatment duration, and patient disposition

Patients received BRV at a median modal dose of 150 mg/day (range 20–200 mg/day) for a median treatment duration of 2.5 years (range $<$ 0.1–11.3 years; ES). In the SS ($n = 313$), the proportion of patients with a modal dose of BRV $\leq$ 100, $>$ 100 to $<$ 200, and 200 mg/day, was 31.6%, 30.0%, and 38.3%, respectively. The proportion of patients in the ES with a modal dose of BRV $\leq$ 100, $>$ 100 to $<$ 200, and 200 mg/day, was 30.3%, 29.2%, and 40.5%, respectively, with a median treatment duration of 0.9 years, 2.8 years, and 2.8 years, respectively (ES). The overall median starting dose was 100 mg/day ($n = 284$; ES); for patients with a modal dose of BRV $\leq$ 100, $>$ 100 to $<$ 200, and 200 mg/day, the median starting dose of BRV was 75 mg/day, 75 mg/day, and 150 mg/day, respectively.

One hundred and seventy-five (61.6%) patients discontinued BRV. The main reasons for discontinuation ($\geq$ 10% of patients) overall were AE (52 [18.3%]), lack of efficacy (52 [18.3%]), and consent withdrawn (33 [11.6%]) (Supplementary Fig. 1). During the first year of BRV treatment, 91 (32.0%) patients discontinued; the main reasons ($\geq$ 5% of patients) for BRV discontinuation in the first year were AE (12.0%) and lack of efficacy (7.0%). A higher proportion of patients with a BRV modal dose of $\leq$ 100 mg/day discontinued due to AE, with the majority discontinuing during the first year of BRV treatment, compared to patients with higher BRV modal doses (Supplementary Fig. 1).

The KM-estimated time to discontinuation of BRV due to AE or lack of efficacy were generally similar, with a slightly higher proportion of patients discontinuing due to AE during the initial months of BRV treatment (Supplementary Fig. 2). Overall, the median time to discontinuation of BRV due to any reason was 358.5 (range 2–2754) days, due to lack of efficacy was 446.5 (range 34–1957) days, due to AE was 196.5 (range 2–2754) days, and due to lack of efficacy or AE was 343.5 (range 2–2754) days. During the first year of BRV treatment, the overall median time to BRV discontinuation was 144 days; it was shorter in patients with a BRV modal dose $\leq$ 100 mg/day (106 days) compared to those with a BRV modal dose of $>$ 100 to $<$ 200 mg/day (183 days) or 200 mg/day (207 days).

The KM-estimated proportion of patients remaining on BRV treatment at 1, 3, and 5 years, were 69.3%, 48.2%, and 37.3%, respectively. The KM-estimated proportion of patients not discontinuing BRV due to lack of efficacy at 1, 3, and 5 years, were 91.5%, 78.5%, and 73.1%. The KM-estimated proportion of patients not discontinuing BRV due to AE at 1, 3, and 5 years, were 87.4%, 81.4%, and 78.3%. The KM-estimated proportion of patients not discontinuing BRV due to lack of efficacy or AE at 1, 3, and 5 years, were 80.0%, 63.9%, and 57.2%.

3.3. Efficacy of BRV overall, by modal dose, and by completer cohort

The median percentage reduction in FBTCS frequency from baseline was 76.2%. The 50% and 75% responder rates in FBTCS were 68.7% and 50.7%, respectively. In the overall FBTCS population, the median percentage FBTCS reduction, 50% responder rate, and 75% responder rate were numerically lower in patients with a BRV modal dose $\leq$ 100 mg/day than those with higher BRV modal doses.

In the 1-year ($n = 193$), 2-year ($n = 158$), 3-year ($n = 116$), 4-year ($n = 70$), and 5-year ($n = 43$) completer cohorts, the median percentage reductions in FBTCS frequency from baseline (core trial) were 77.4%, 82.0%, 86.3%, 88.3%, and 90.5%, respectively (Fig. 1A). The 50% responder rates were 75.1%, 77.2%, 78.4%, 80.0%, and 79.1% (Fig. 1B). The 75% responder rates were 53.4%, 58.2%, 62.1%, 62.9%, and 65.1% (Fig. 1C). In each completer cohort the efficacy of BRV was maintained over time (Supplementary Fig. 3).

Table 1
Baseline demographics and epilepsy characteristics overall and by BRV modal dose category[a].

BRV modal dose category	Efficacy Set excluding patients on concomitant LEV				Safety Set including patients on concomitant LEV			
	BRV Overall (*N* = 284)	BRV ≤ 100 mg/day (*n* = 86)	BRV > 100 to < 200 mg/day (*n* = 83)	BRV 200 mg/day (*n* = 115)	BRV Overall (*N* = 313)	BRV ≤ 100 mg/day (*n* = 99)	BRV > 100 to < 200 mg/day (*n* = 94)	BRV 200 mg/day (*n* = 120)
Age, mean (SD), years	37.0 (12.5)	36.1 (12.7)	37.6 (13.1)	37.2 (11.9)	37.3 (12.6)	36.6 (12.8)	37.6 (13.0)	37.6 (12.1)
Male, *n* (%)	147 (51.8)	46 (53.5)	42 (50.6)	59 (51.3)	161 (51.4)	53 (53.5)	48 (51.1)	60 (50.0)
Age at onset of epilepsy, mean (SD), years	15.1 (13.0)	14.5 (13.9)	14.8 (12.6)	15.9 (12.6)	15.0 (13.0)	14.2 (13.8)	14.7 (12.5)	15.9 (12.8)
Duration of epilepsy, mean (SD), years	22.4 (12.8)	22.2 (11.9)	23.4 (13.3)	21.8 (13.1)	22.9 (13.2)	23.0 (12.6)	23.5 (13.3)	22.3 (13.5)
Baseline focal seizure frequency per 28 days, median (range)	8.3 (2.9–494.2)	9.7 (3.8–135.5)	7.1 (3.6–143.8)	8.0 (2.9–494.2)	8.5 (2.9–494.2)	9.4 (3.6–135.5)	7.1 (3.5–143.8)	8.0 (2.9–494.2)
Baseline FBTCS frequency per 28 days, median (range)	2.8 (0.4–41.1)	3.5 (0.4–41.1)	3.0 (0.4–25.3)	2.0 (0.4–27.5)	2.8 (0.4–41.1)	3.3 (0.4–41.1)	3.0 (0.4–25.3)	2.0 (0.4–27.5)
Seizure classification[b], *n* (%)								
Secondary generalized (*FBTCS*) only	52 (18.3)	19 (22.1)	18 (21.7)	15 (13.0)	57 (18.2)	19 (19.2)	22 (23.4)	16 (13.3)
Secondary generalized (*FBTCS*) and simple partial (*focal aware*)	28 (9.9)	8 (9.3)	8 (9.6)	12 (10.4)	30 (9.6)	9 (9.1)	8 (8.5)	13 (10.8)
Secondary generalized (*FBTCS*) and complex partial (*focal impaired awareness*)	149 (52.5)	39 (45.3)	47 (56.6)	63 (54.8)	167 (53.4)	48 (48.5)	54 (57.4)	65 (54.2)
Secondary generalized (*FBTCS*), simple partial (*focal aware*), and complex partial (*focal impaired awareness*)	55 (19.4)	20 (23.3)	10 (12.0)	25 (21.7)	59 (18.8)	23 (23.2)	10 (10.6)	26 (21.7)
Number of prior ASMs[c], *n* (%)								
0–1	77 (27.1)	22 (25.6)	33 (39.8)	22 (19.1)	81 (25.9)	24 (24.2)	33 (35.1)	24 (20.0)
2–4	110 (38.7)	38 (44.2)	28 (33.7)	44 (38.3)	126 (40.3)	44 (44.4)	36 (38.3)	46 (38.3)
≥ 5	97 (34.2)	26 (30.2)	22 (26.5)	49 (42.6)	106 (33.9)	31 (31.3)	25 (26.6)	50 (41.7)
Number of concomitant ASMs at BRV initiation[d], *n* (%)								
0	1 (0.4)	1 (1.2)	0	0	1 (0.3)	1 (1.0)	0	0
1	69 (24.3)	18 (20.9)	18 (21.7)	33 (28.7)	73 (23.3)	19 (19.2)	20 (21.3)	34 (28.3)
2	208 (73.2)	64 (74.4)	64 (77.1)	80 (69.6)	232 (74.1)	75 (75.8)	73 (77.7)	84 (70.0)
≥ 3	6 (2.1)	3 (3.5)	1 (1.2)	2 (1.7)	7 (2.2)	4 (4.0)	1 (1.1)	2 (1.7)
Concomitant ASMs at BRV initiation, taken by ≥ 10 of all patients, *n* (%)								
Carbamazepine	109 (38.4)	30 (34.9)	35 (42.2)	44 (38.3)	118 (37.7)	33 (33.3)	38 (40.4)	47 (39.2)
Valproate	93 (32.7)	32 (37.2)	28 (33.7)	33 (28.7)	97 (31.0)	34 (34.3)	30 (31.9)	33 (27.5)
Lamotrigine	63 (22.2)	16 (18.6)	19 (22.9)	28 (24.3)	70 (22.4)	19 (19.2)	20 (21.3)	31 (25.8)
Oxcarbazepine	46 (16.2)	15 (17.4)	14 (16.9)	17 (14.8)	51 (16.3)	18 (18.2)	16 (17.0)	17 (14.2)
Topiramate	38 (13.4)	12 (14.0)	12 (14.5)	14 (12.2)	42 (13.4)	13 (13.1)	13 (13.8)	16 (13.3)
Phenytoin	36 (12.7)	12 (14.0)	11 (13.3)	13 (11.3)	39 (12.5)	14 (14.1)	12 (12.8)	13 (10.8)
BRV initiation period								
Core trial, *n* (%)	229 (80.6)	79 (91.9)	59 (71.1)	91 (79.1)	254 (81.2)	91 (91.9)	68 (72.3)	95 (79.2)
Long-term follow-up trial, *n* (%)	55 (19.4)	7 (8.1)	24 (28.9)	24 (20.9)	59 (18.8)	8 (8.1)	26 (27.7)	25 (20.8)
Patient entered long-term follow-up trial, *n* (%)	253 (89.1)	66 (76.7)	83 (100)	104 (90.4)	280 (89.5)	77 (77.8)	94 (100)	109 (90.8)
Concomitant LEV at BRV initiation, *n* (%)	–	–	–	–	17 (5.4)	10 (10.1)	7 (7.4)	0
Concomitant LEV at any time during the trial, *n* (%)	–	–	–	–	29 (9.3)	13 (13.1)	11 (11.7)	5 (4.2)

ASM, antiseizure medication; FBTCS, focal to bilateral tonic-clonic seizures; LEV, levetiracetam; SD, standard deviation.

[a] Patients with an initial BRV dose of 50–200 mg/day during either the core or long-term follow-up trial.

[b] Seizure types are listed per the International League Against Epilepsy 1981 classification (Commission on Classification and Terminology of the International League Against Epilepsy, 1981) as per the trial protocol, with the newer terminology (Fisher et al., 2017) provided in parentheses.

[c] Prior ASMs were ASMs discontinued before BRV initiation (in the core or long-term follow-up trial). Trials N01252 and N01253 collected ASM use within the 5 years before trial entry, whereas trial N01358 collected all history of ASMs used before trial entry.

[d] One patient randomized to placebo (N01252) was taking lamotrigine and oxcarbazepine that were discontinued 9 days before BRV initiation and recommenced on the day of BRV initiation.

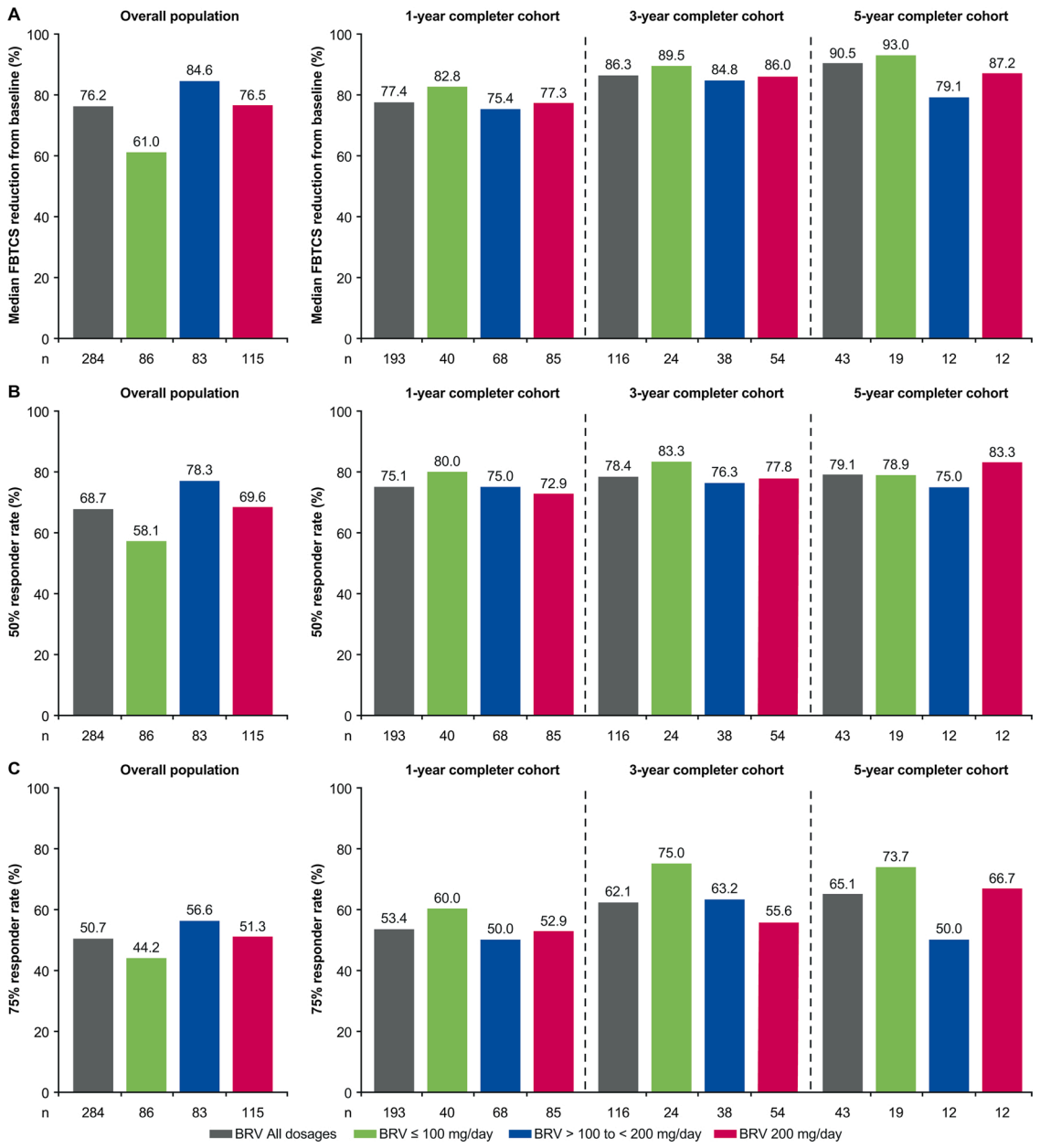

Fig. 1. Efficacy of BRV for the overall population and yearly completer cohorts by BRV all dosages and modal dose: (A) median percentage reduction from baseline of the core trial in FBTCS frequency per 28 days, (B) 50% responder rate, and (C) 75% responder rate (ES).
BRV, brivaracetam; ES, Efficacy Set; FBTCS, focal to bilateral tonic-clonic seizures.

3.4. Time to sustained response during the first year of adjunctive BRV treatment

KM estimates of the time to sustained 50%, 75%, and 100% response in FBTCS during the first year of treatment overall and by BRV modal dose category showed maintenance or improvements in the response to BRV over time (Fig. 2). Sustained ≥ 50%, ≥ 75%, and 100% response in FBTCS from day 1 of adjunctive BRV treatment during the entire first year was estimated for 32.5%, 21.1%, and 15.0% of patients overall, respectively.

The estimated proportion of patients achieving a sustained response in FBTCS generally increased over time with 51.1% and 36.3% of patients classified as ≥ 50% and ≥ 75% responders at day 364. The estimated proportion of patients achieving ≥ 50% or ≥ 75% sustained response in FBTCS increased mainly during the first 6 months of treatment (more pronounced for ≥ 50% response). The estimated proportion of patients achieving sustained 100% response in FBTCS was stable from the day 1 to day 364 of BRV treatment. The proportion of patients who achieved sustained response during the first year of adjunctive BRV treatment was highest for patients with a BRV modal dose of > 100 to < 200 mg/day, followed by 200 mg/day, and was lowest for patients with a BRV modal dose ≤ 100 mg/day.

3.5. Freedom from FBTCS

Overall, 34.9% of patients were free from FBTCS for ≥ 1 year at any time during the entire treatment period. For patients with at least 1 year of BRV exposure (n = 193), overall 51.3% were free from FBTCS for ≥ 1 year during the entire treatment period. This proportion was similar for patients with a BRV modal dose of ≤ 100, > 100 to < 200, and 200 mg/day, with 52.5%, 55.9%, and 47.1% of patients free from FBTCS for ≥ 1 year, respectively. For the patients who completed at least 1 year of BRV

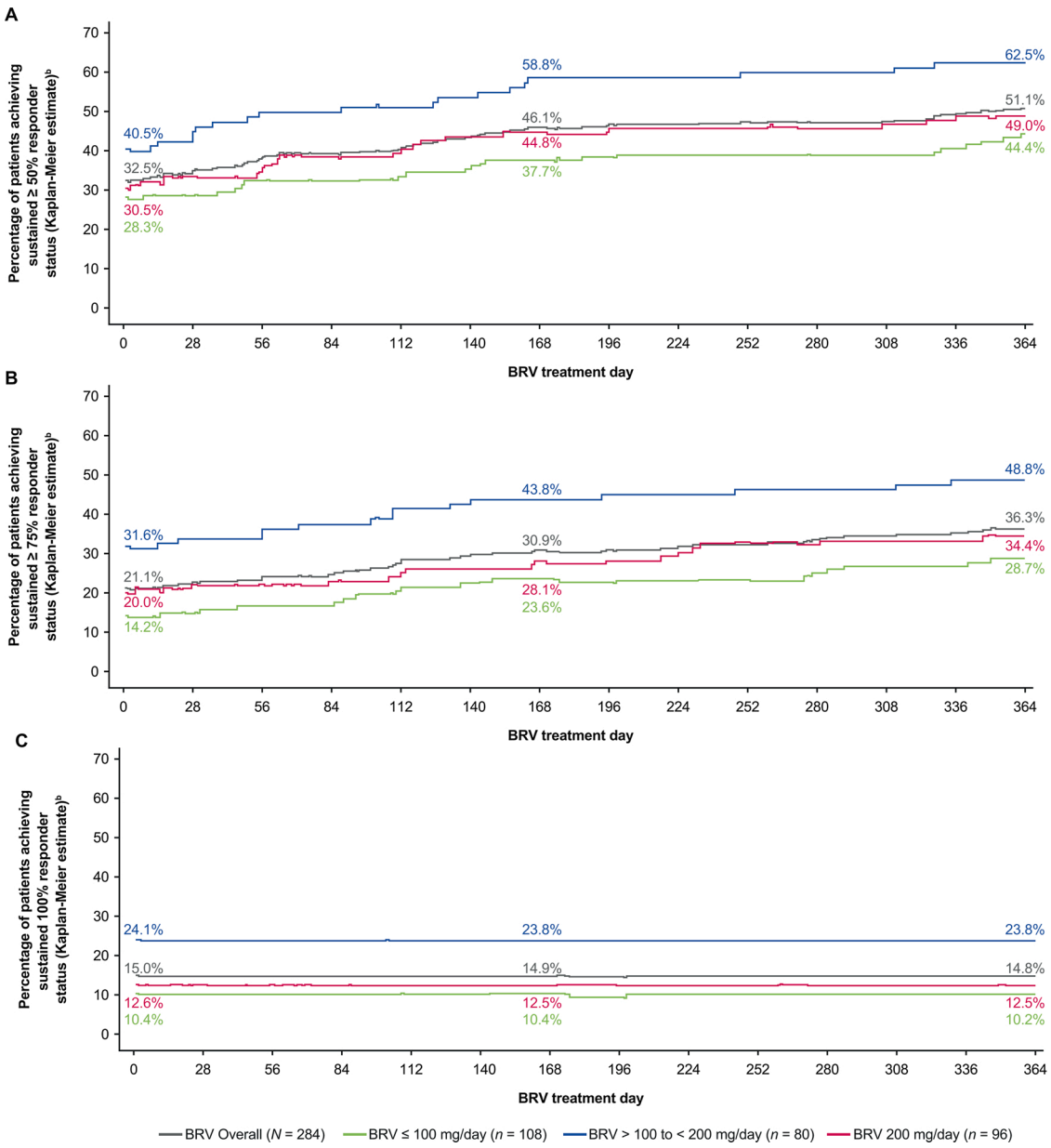

Fig. 2. Kaplan-Meier estimated time to sustained (A) ≥ 50%, (B) ≥ 75%, and (C) 100% response in FBTCS during the first year of BRV treatment: overall and by BRV modal dose[a] (ES).

BRV, brivaracetam; ES, Efficacy Set; FBTCS, focal to bilateral tonic-clonic seizures.

[a] The modal dose was based on the BRV dose taken during the first year of BRV exposure.

[b] Kaplan-Meier estimates of the percentage of patients who achieved sustained response in FBTCS during the first year of BRV treatment. Patients who prematurely discontinued the trial during the first year after BRV initiation were classified as nonresponders for the entire evaluation period.

treatment, 22.3% were free from FBTCS for at least 1 year from the first day of BRV treatment. For patients with at least 5 years of BRV exposure (n = 43), 11.6% were free from FBTCS for at least 5 years from the first day of BRV treatment (Supplementary Fig. 4).

Within each yearly completer cohort, the proportion of patients reporting no FBTCS generally increased over time, and the proportion of patients reporting one to two FBTCS generally decreased over time (Fig. 3). In patients with at least 1 year of adjunctive BRV treatment, 22.8% of patients did not report FBTCS during the first year from the first day of treatment, and this proportion ranged between 22.2% and 23.3% across the 1-, 2-, 3-, 4-, and 5-year completer cohorts. In patients with at least 2 years of BRV treatment, 36.1%, 36.2%, 35.7%, and 34.9% of patients in the 2-, 3-, 4-, and 5-year completer cohorts, respectively, did not report FBTCS during the second year of BRV treatment.

3.6. Efficacy of BRV in FBTCS by number of prior or concomitant ASMs, age at epilepsy onset, and epilepsy duration

Numerically higher FBTCS efficacy response was observed in patients with fewer prior ASMs taken and discontinued before BRV initiation and in patients on one versus two concomitant ASMs at BRV initiation (Supplementary Fig. 5). No differences were observed in the median percentage reduction from baseline and 75% responder rate based on age at epilepsy onset. However, a numerically lower 50% responder rate and freedom from FBTCS for at least 1 year were observed in patients with epilepsy onset at ≥ 20 years of age compared to patients with earlier epilepsy onset. Patients with a longer epilepsy duration showed a numerically higher efficacy response in most of the outcomes assessed.

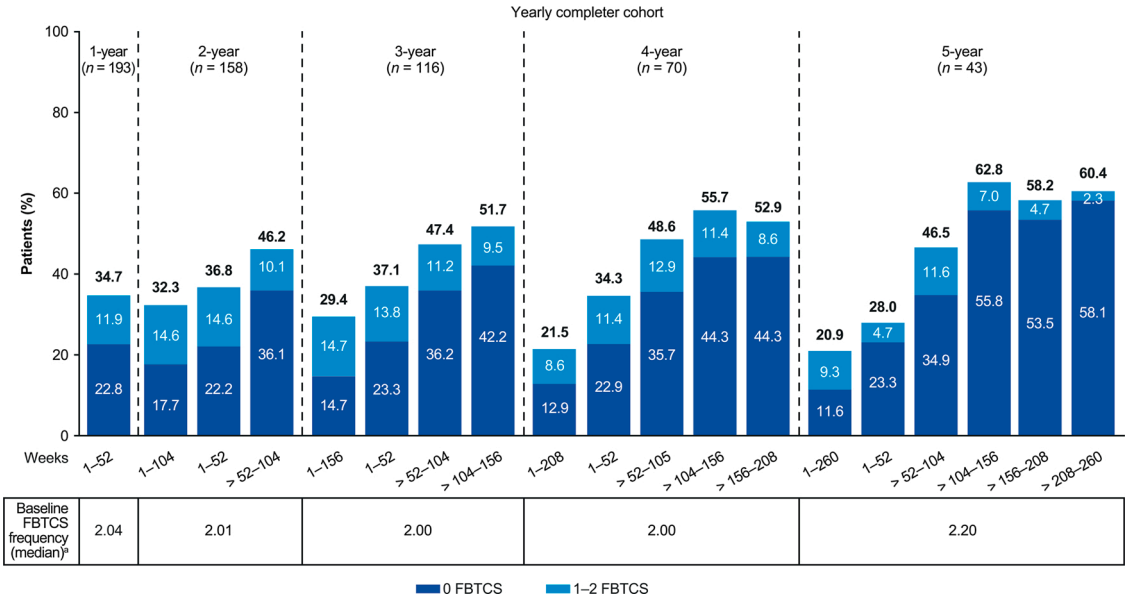

Fig. 3. Proportion of patients with none or one to two FBTCS by yearly completer cohort and 52-week interval (ES).
ES, Efficacy Set; FBTCS, focal to bilateral tonic-clonic seizures.
[a] Seizure frequency is standardized to a 28-day frequency.

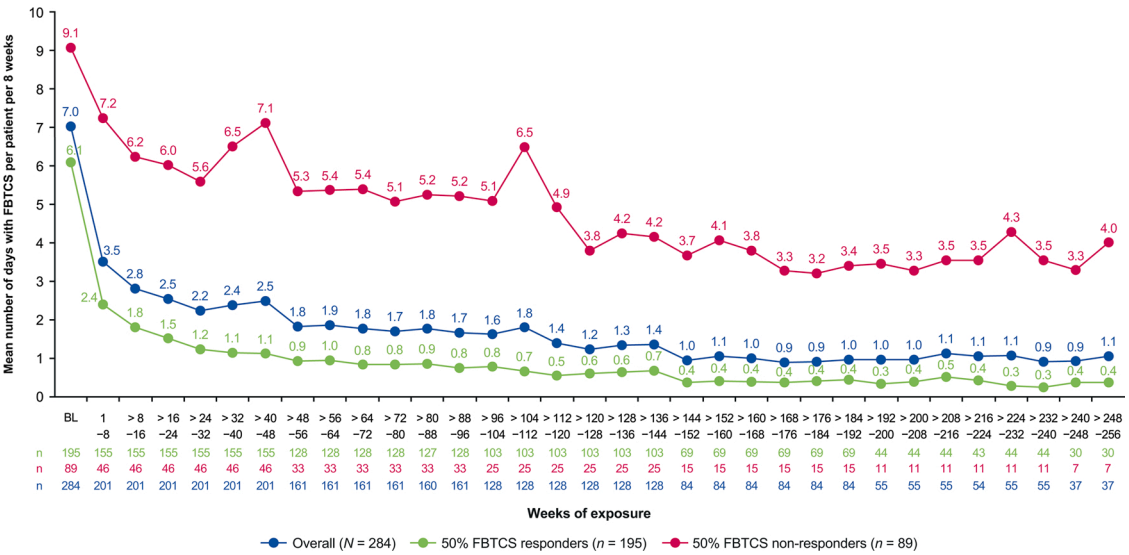

Fig. 4. Mean number of days with FBTCS per patient per 8 weeks during the 8-week baseline and by 8-week intervals during BRV treatment (overall and by 50% responder status) in patients with FBTCS during the core trial baseline (ES).
BL, baseline; BRV, brivaracetam; ES, Efficacy Set; FBTCS, focal to bilateral tonic-clonic seizures.

3.7. Number of days with FBTCS per 8-week intervals

In the overall population the mean number of days with FBTCS per patient per 8-week interval was consistently substantially lower during long-term adjunctive BRV treatment (range 0.9–3.5) compared with the 8-week baseline (7.0) (Fig. 4). The decrease in the mean number of days with FBTCS was more pronounced in 50% responders. However, a decrease was also observed in the patients who did not qualify as 50% responders. Within each yearly completer cohort, the mean number of days with FBTCS during adjunctive BRV treatment decreased compared with baseline and was generally stable over time (Supplementary Fig. 6).

3.8. Time to onset of FBTCS

Overall, there was a substantially higher mean time from BRV initiation to first FBTCS (222.2 days; 95% CI: 161.3, 283.0) compared with the mean time from last FBTCS to BRV initiation (17.5 days; 95% CI: 14.9, 20.0) and from baseline start to first FBTCS (12.1 days; 95% CI: 10.5, 13.7) (Fig. 5).

3.9. QOLIE-31-P scores

Patients who received BRV for ≥ 1 or ≥ 2 years showed improvements in the mean total QOLIE-31-P score, with a considerable mean improvement at 2 years; 43.6% and 46.4% of patients showed clinically meaningful improvements in total QOLIE-31-P score after 1 and 2 years of treatment, respectively (Supplementary Fig. 7). The largest improvements and > 50% of patients reporting a clinically meaningful improvement in the QOLIE-31-P score were observed in the seizure worry and daily activities/social functioning subscales after 1 and 2

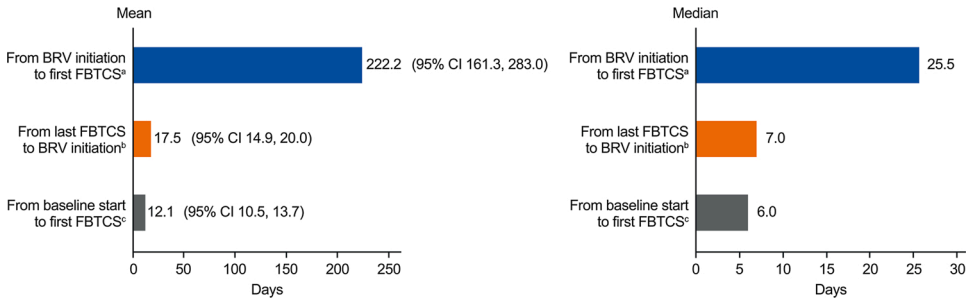

Fig. 5. Time to first FBTCS during baseline and BRV treatment, and time from last FBTCS to BRV initiation, in patients with FBTCS during the core trial baseline (ES).
BRV, brivaracetam; CI, confidence interval; ES, Efficacy Set; FBTCS, focal to bilateral tonic-clonic seizures.
[a] Measured from BRV initiation and censored at the end of BRV treatment for patients who did not report FBTCS.
[b] Measured from baseline for patients randomized to BRV in the core trial, and from across baseline and the core trial for patients randomized to placebo in the core trial.
[c] Measured from the start of baseline.

years of BRV treatment, and in the medication effects subscale after 2 years of BRV treatment. Clinically meaningful improvement in the cognitive functioning subscale was reported by 45.8% and 47.2% of patients at 1 and 2 years of BRV treatment, respectively.

3.10. Tolerability

In the SS ($n = 313$), 278 (88.8%) patients reported at least one TEAE, 88 (28.1%) patients had a serious TEAE, and 55 (17.6%) discontinued due to a TEAE (Table 2). The most frequent TEAEs (≥ 10% of patients) were headache (18.2%), dizziness (14.4%), somnolence (14.4%), fatigue (11.8%), and convulsion (10.5%). One hundred and seventy (54.3%) patients had a TEAE that was considered drug-related by the investigator, most commonly (≥ 5% of patients) somnolence (38 [12.1%]), dizziness (28 [8.9%]), fatigue (27 [8.6%]), and headache (19 [6.1%]). At least one severe TEAE was reported by 83 (26.5%) patients, and the most common (≥ 1% of patients) were convulsion (eight [2.6%]), status epilepticus (eight [2.6%]), headache (five [1.6%]), psychotic disorder (four [1.3%]), fatigue (three [1.0%]), epilepsy (three [1.0%]), and suicide attempt (three [1.0%]).

Serious TEAEs reported by four or more patients were convulsion (10 [3.2%]), status epilepticus (nine [2.9%]), suicide attempt (five [1.6%]), epilepsy (four [1.3%]), psychotic disorder (four [1.3%]), and hyponatremia (four [1.3%]).

The most common (≥ 1% of patients) TEAEs leading to permanent discontinuation of BRV were dizziness (five [1.6%]), suicide attempt (four [1.3%]), and convulsion (three [1.0%]).

Psychiatric TEAEs and TEAEs potentially associated with behavioral disorders were reported by 101 (32.3%) and 42 (13.4%) patients, respectively, and were most commonly (≥ 2% of all patients) irritability (6.7%), insomnia (6.4%), depression (6.1%), anxiety (5.8%), and aggression (3.8%). During long-term adjunctive BRV treatment (up to 11.3 years) in adults with FBTCS, 11 (3.5%) patients died (SS: MedDRA Preferred Terms: death [two patients], cardio-respiratory arrest, sudden

Table 2
Incidence of TEAEs with onset during the treatment period overall and by BRV modal dose category (SS).

Patients, *n* (%)	BRV Overall ($N = 313$)	BRV ≤ 100 mg/day ($n = 99$)	BRV > 100 to < 200 mg/day ($n = 94$)	BRV 200 mg/day ($n = 120$)
Any TEAEs	278 (88.8)	90 (90.9)	82 (87.2)	106 (88.3)
Drug-related TEAEs	170 (54.3)	68 (68.7)	43 (45.7)	59 (49.2)
Serious TEAEs	88 (28.1)	30 (30.3)	26 (27.7)	32 (26.7)
Severe TEAEs	83 (26.5)	29 (29.3)	20 (21.3)	34 (28.3)
Discontinuations due to TEAEs	55 (17.6)	28 (28.3)	9 (9.6)	18 (15.0)
Deaths	11 (3.5)	5 (5.1)	3 (3.2)	3 (2.5)
TEAEs[a] occurring in ≥ 10% of all patients				
Headache	57 (18.2)	21 (21.2)	16 (17.0)	20 (16.7)
Dizziness	45 (14.4)	12 (12.1)	9 (9.6)	24 (20.0)
Somnolence	45 (14.4)	16 (16.2)	9 (9.6)	20 (16.7)
Fatigue	37 (11.8)	12 (12.1)	9 (9.6)	16 (13.3)
Convulsion	33 (10.5)	14 (14.1)	13 (13.8)	6 (5.0)
TEAEs classified as psychiatric disorders[a]				
At least one	101 (32.3)	38 (38.4)	29 (30.9)	34 (28.3)
Drug-related	62 (19.8)	32 (32.3)	16 (17.0)	14 (11.7)
Leading to discontinuation	20 (6.4)	12 (12.1)	2 (2.1)	6 (5.0)
TEAEs potentially associated with behavioral disorders[b]				
At least one	42 (13.4)	19 (19.2)	8 (8.5)	15 (12.5)
Drug-related	26 (8.3)	15 (15.2)	4 (4.3)	7 (5.8)
Leading to discontinuation	7 (2.2)	4 (4.0)	1 (1.1)	2 (1.7)
TEAEs classified as psychiatric disorders[a] and potentially associated with behavioral disorders[b] reported by ≥ 2% of all patients				
Irritability	21 (6.7)	8 (8.1)	4 (4.3)	9 (7.5)
Insomnia	20 (6.4)	9 (9.1)	4 (4.3)	7 (5.8)
Depression	19 (6.1)	7 (7.1)	6 (6.4)	6 (5.0)
Anxiety	18 (5.8)	5 (5.1)	7 (7.4)	6 (5.0)
Aggression	12 (3.8)	7 (7.1)	3 (3.2)	2 (1.7)

SS, Safety Set; TEAE, treatment-emergent adverse event.
[a] Preferred Term (Medical Dictionary for Regulatory Activities, Version 15.0).
[b] Medical Dictionary for Regulatory Activities Preferred Terms selected by medical review.

death, SUDEP, head injury, intentional overdose, road traffic accident, central nervous system lesion, completed suicide, and brain hypoxia [one patient each]). Three deaths were considered drug-related by the investigator (MedDRA Preferred Terms: death, completed suicide, and brain hypoxia), and all other deaths were not considered drug-related.

In patients without a history of FBTCS the incidence of new-onset FBTCS during BRV treatment was low; 25/405 (6.2%) patients reported their first FBTCS during BRV treatment, with a mean time from BRV initiation of 463.6 days (95% CI: 246.2, 681.0; median: 212.0 days); 3/405 (0.7%) patients reported a TEAE of grand mal convulsion during BRV treatment at day 12, 367, and 1123 after BRV initiation, respectively.

4. Discussion

The results of this post hoc analysis of long-term (up to 11.3 years) pooled data indicate the long-term sustained efficacy of adjunctive BRV in reducing the frequency of FBTCS in adults. In patients with FBTCS, long-term BRV treatment was generally well tolerated and associated with improvement in the overall HRQoL. The results from this analysis extends the previous findings on the short-term (12-week) efficacy and tolerability of adjunctive BRV in adults with FBTCS (Klein et al., 2020a; Moseley et al., 2016) by reporting long-term efficacy, tolerability, and HRQoL data.

Although randomized, controlled trials are the standard for evaluating the efficacy and safety of new drugs (Maguire et al., 2008), open-label, long-term follow-up trials can provide valuable information in a setting that more closely emulates clinical practice regarding long-term tolerability and efficacy of ASMs (Hemming et al., 2008; Maguire et al., 2008; Mohanraj and Brodie, 2003). The results from this post hoc analysis therefore provide important data on the long-term efficacy and tolerability of BRV in patients with FBTCS.

The median BRV treatment duration was 2.5 years (range < 0.1–11.3 years) and the estimated proportion of patients remaining on BRV treatment at 1, 3, and 5 years, was 69.3%, 48.2%, and 37.3%, respectively. The same proportion of patients discontinued due to lack of efficacy (18.3%) or AE (18.3%). The estimated proportion of patients not discontinuing BRV due to lack of efficacy or AE was 80.0%, 63.9%, and 57.2% at 1, 3, and 5 years, respectively. As 11.6% of patients discontinued treatment due to consent withdrawn, it cannot be ruled out that some of these patients may have discontinued BRV treatment due to reasons related to lack of efficacy or AEs. Although this is a potential limitation, considering the conservative approach applied in assessing the time to BRV discontinuation (measured from the first day of active treatment whether during the core trial or at long-term follow-up trial entry), these data support the long-term effectiveness of BRV in adults with FBTCS.

In order to evaluate the efficacy response during adjunctive BRV treatment over time, different approaches were applied. The time to sustained FBTCS response (50%, 75%, and 100%) during the first year of treatment estimated the proportion of patients who achieved a sustained (rather than transient) response and did not discontinue BRV during the first year of treatment (Klein et al., 2017, 2020a). In the population with FBTCS analyzed, approximately one-third of patients with FBTCS treated with BRV achieved sustained ≥ 50% response, one-fifth achieved sustained ≥ 75% response, and one-seventh achieved sustained 100% response in FBTCS on the first-treatment day through the entire first year of treatment. For time to sustained ≥ 50% response during the first year, the proportion of patients achieving a sustained response increased mainly during the first 6 months of treatment, with a smaller further increase during the second 6 months. This result suggests that the majority of patients who will achieve a sustained ≥ 50% response during the first year of BRV treatment will reach this outcome during the first 6 months of treatment. These data further support previous observations that efficacy of BRV occurs early after BRV is initiated (Klein et al., 2017, 2020a; Klein et al., 2020b) and provide data over a longer BRV treatment period (1 year).

For patients who completed ≥ 1 year of adjunctive BRV treatment, analyses were performed on early completer cohorts (1-year to 5-year completer cohorts), where the same patients were followed from the beginning to the end of the particular period (during the overall period and by 12-week intervals). This approach, ensuring no within-cohort selection bias (Ben-Menachem et al., 2003), showed that the FBTCS response (median percentage reduction from baseline, 50%, and 75% responder rates) in each cohort was maintained over time.

In the overall population, the time to sustained response in FBTCS during the first year of treatment tended to be lower for patients who received a modal dose of BRV ≤ 100 mg/day. However, when considering the patients with a modal BRV dose ≤ 100 mg/day who completed at least 1 year of treatment, the efficacy outcomes were generally similar (or numerically higher) to those observed in patients with BRV modal doses > 100 mg/day. The disposition data during the first year of BRV treatment showed that a higher proportion of patients with a BRV modal dose ≤ 100 mg/day compared to those with a BRV modal dose > 100 to < 200 mg/day and 200 mg/day discontinued treatment due to any reason (53.5% vs 18.1% and 26.1%), due to AE (20.9% vs 4.8% and 10.4%), or due to lack of efficacy (14.0% vs 2.4% and 5.2%). These data suggest that the patients treated with a BRV modal dose ≤ 100 mg/day consisted of patients that were more sensitive to AEs and/or were more difficult to control, and patients who responded to relatively low BRV doses.

Several studies have identified that the presence and frequency of generalized tonic-clonic seizures (GTCS) is the most important risk factor for SUDEP (Sveinsson et al., 2020), with an increasing number of GTCS per year associated with a statistically significant increased risk for SUDEP (Hesdorffer et al., 2011; Ryvlin et al., 2019). Patients with three or more GTCS per year have a 15-fold increased risk of SUDEP (Harden et al., 2017). In this post hoc analysis, 34.9% of patients were free from FBTCS for ≥ 1 year at any time during the entire treatment period; in patients who completed at least 1 year of adjunctive BRV treatment (median baseline FBTCS frequency of approximately two per 28 days), 51.3% were free from FBTCS for ≥ 1 year during the entire treatment period; approximately 23% were free from FBTCS during the first year (from the first day of BRV treatment), and approximately 36% did not report FBTCS during the second year of BRV treatment. Therefore, the maintenance or improvement in the proportion of patients not reporting FBTCS over time presented in this pooled analysis supports the beneficial effects of BRV over time.

The occurrence of GTCS has been identified as one of the factors predicting poor HRQoL (de la Loge et al., 2016), and reducing the frequency of FBTCS has the potential to improve the overall HRQoL of patients with epilepsy (Sperling et al., 2016; Taylor et al., 2011). In this analysis in patients with FBTCS, long-term adjunctive BRV treatment was generally associated with improvement in the overall HRQoL. The largest improvements in the QOLIE-31-P scores after 1 and 2 years of adjunctive BRV treatment were observed in the subscales sensitive to efficacy (seizure worry and daily activities/social functioning), reflecting the long-term efficacy of adjunctive BRV. Clinically meaningful improvement was also reported by 52.8% of patients in the medication effects subscale after 2 years of treatment, reflecting a low level of tolerability issues with BRV treatment. For the QOLIE-31-P total score and subscale results, the mean change from baseline and the proportion of patients with a meaningful improvement, are similar to those reported for adults with uncontrolled focal onset (partial) seizures receiving adjunctive BRV in a pooled analysis of Phase IIb/III and long-term follow-up trials (Toledo et al., 2016), as well as in an interim analysis of an ongoing prospective, non-interventional post-marketing study on patients in Europe (EP0077; NCT02687711) (Steinhoff et al., 2020). These QOLIE-31-P data provide further evidence that long-term treatment with adjunctive BRV in patients with FBTCS leads to improvements in quality of life measures.

In this post hoc analysis, at least one TEAE was reported by 88.8% of

patients with FBTCS, 17.6% of patients discontinued due to a TEAE, and the most commonly reported TEAEs (≥ 10%) were headache, dizziness, somnolence, fatigue, and convulsion. Therefore, the tolerability profile of BRV in this subpopulation with FBTCS was generally similar to that reported in a pooled interim analysis of Phase IIb/III and long-term follow-up trials of adjunctive BRV in patients with focal or generalized seizures (Toledo et al., 2016).

Behavioral TEAEs such as aggression and anger have been often associated with ASM use (Chen et al., 2017). During long-term BRV treatment of patients with FBTCS, the incidence of TEAEs potentially associated with behavioral disorders was generally low (13.4%), and was comparable with the incidence reported in pooled open-label, long-term trials of BRV in adults with epilepsy (15.1%) (UCB Pharma, 2020).

Some caution is recommended in interpreting these data, as this was a post hoc analysis of data pooled across double-blind and single-arm open-label, long-term follow-up trials without a comparator group. As BRV was used as an adjunctive treatment and in the long-term follow-up trials a flexible dose regimen of BRV and the concomitant ASM(s) was applied, the potential contribution of adaptations in the treatment regimen of the concomitant ASM(s) to the efficacy outcomes observed and the TEAEs reported cannot be completely ignored.

In summary, long-term adjunctive BRV treatment was generally well tolerated and provided sustained long-term reduction in the frequency of FBTCS in adults, with 22.8% of patients who completed at least 1 year of BRV treatment and did not report FBTCS during the first year from the first day of BRV treatment.

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 executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password protected portal.

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Declaration of Competing Interest

Brian D Moseley has served as a paid consultant for Eisai, LivaNova, UCB Pharma, and Validus Pharmaceuticals; serves on speaker bureaus for Eisai, LivaNova, and UCB Pharma; and has received research support from LivaNova, Nonin Medical, Inc., Sunovion, and Xenon Pharmaceuticals Inc. Ali A Asadi-Pooya has acted as a consultant for UCB Pharma; has received honoraria from Cobel Darou, RaymandRad, Sanofi, and Tekaje; has received royalty from Oxford University Press (book publication), and a grant from the National Institute for Medical Research Development. Svetlana Dimova, Sami Elmoufti, and Cédric Laloyaux are employees of UCB Pharma.

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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.2021.106694.

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