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Effectiveness and tolerability of adjunctive brivaracetam in patients with focal seizures: Second interim analysis of 6-month data from a prospective observational study in Europe

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ABSTRACT

Brivaracetam (BRV) is indicated for adjunctive treatment of focal (partial-onset) seizures with or without secondary generalisation in patients 4 years of age and older in the European Union (EU). An ongoing 12-month, prospective, non-interventional post-marketing study (EP0077; NCT02687711) is collecting real-world information on patients receiving treatment with adjunctive BRV in Europe. In this study, BRV is prescribed according to routine clinical practice and the EU Summary of Product Characteristics. This second interim analysis assessed effectiveness, tolerability and health-related quality of life outcomes for up to 6 months of treatment.

At the cut-off date (13 April 2018), 266 patients from five countries had attended Visit 1, 24.1 % (64/266) had completed the study, 37.6 % (100/266) were ongoing, and 38.3 % (102/266) had discontinued. In total, 261 patients had at least one dose of BRV and were included in the analyses. Patients had a mean time since epilepsy diagnosis of 23.2 years, a mean of eight lifetime AEDs (sum of AEDs discontinued prior to study entry and concomitant at study entry), and a median of five focal seizures per 28 days during the 3-month retrospective Baseline. 66.3 % of patients initiated BRV at a dose within the recommended starting range (50–100 mg/day) and 87.1 % of patients received BRV modal doses within the recommended dose range (50–200 mg/day) during the study. Retention rates were 79.1 % (N = 239) at 3 months and 62.1 % (N = 211) at 6 months. The 50 % responder rates for focal seizures were 46.8 % (N = 139) at 3 months and 53.6 % (N = 97) at 6 months. The proportions of patients who were seizure-free were 10.7 % (21/196) and 7.5 % (15/199) at 3 and 6 months of treatment, respectively. Median percent reductions in focal seizure frequency per 28 days from Baseline to 3 and 6 months were 34.6 % (N = 139) and 53.3 % (N = 97), respectively. Overall, 44.2 % of patients had an improvement and 15.4 % had a worsening in Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 total score from Baseline to 6 months (N = 52). At least one treatment-emergent adverse event (TEAE) was reported in 51.0 % (133/261) of patients, and 34.5 % (90/261) of patients had drug-related TEAEs. The most

Abbreviations: AED, antiepileptic drug; CGIC, Clinical Global Impression of Change; CI, confidence interval; FAS, full analysis set; ILAE, International League Against Epilepsy; HRQoL, health-related quality of life; LEV, levetiracetam; MedDRA, Medical Dictionary for Regulatory Activities; mFAS, modified full analysis set; PGIC, Patient's Global Impression of Change; QOLIE-31-P, Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; SD, standard deviation; SGS, secondarily generalised seizures; SmPC, Summary of Product Characteristics; SS, safety set; TEAE, treatment-emergent adverse event

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common drug-related TEAEs (≥5% of patients) were drug ineffective (7.7 %), seizure (6.5 %), and fatigue (6.1 %).

In this 6-month interim analysis, BRV showed effectiveness when used in clinical practice in five European countries. BRV was well tolerated, and no new safety signals were observed.

1. Introduction

Brivaracetam (BRV) is a selective, high-affinity ligand for synaptic vesicle protein 2A (Gillard et al., 2011). Efficacy and tolerability of adjunctive BRV in adults with focal (partial-onset) seizures was established in three randomised, double-blind, placebo-controlled, fixed-dose Phase III trials in patients ≥16 years of age (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). In the European Union (EU), BRV is approved for adjunctive treatment of focal seizures with or without secondary generalisation in patients 4 years of age and older (UCB Pharma, 2018).

This multinational, observational, post-marketing study is designed to collect information on the effectiveness of BRV in patients with focal seizures who are treated in clinical practice. In the first interim analysis, which included mostly patients recruited from Germany (100/109), BRV displayed a tolerability profile consistent with previous data and a discontinuation rate of 36 % (data cut-off: 5 October 2016) (Steinhoff et al., 2017b).

We report data from the second interim analysis, in order to determine the effectiveness, tolerability and health-related quality of life (HRQoL) outcomes in patients ≥16 years of age with focal seizures after receiving 6-month adjunctive treatment with BRV in real-world practice.

2. Methods

2.1. Study design and patients

EP0077 (BASE: **B**rivaracetam **A**nd **S**eizure reduction in **E**pilepsy; ClinicalTrials.gov: NCT02687711) is a 12-month, prospective, non-interventional, post-marketing study. This study is collecting real-world information on the effectiveness, tolerability, and HRQoL of BRV in patients (≥16 years of age) with a clinical diagnosis of focal (partial-onset) seizures (with or without secondary generalisation) who are treated in clinical practice in Europe. The primary outcome of this ongoing study is BRV retention at 12 months of treatment. Study recruitment is planned for 530 patients.

Eligible patients have never been treated with BRV before enrolment in this study, and the decision to prescribe BRV is made by the treating physician, independently of participation in the study. All visits and assessments are scheduled and conducted per routine clinical practice, with visits on the day of first BRV dose, and approximately 3, 6, and 12 months thereafter. Per routine clinical practice, all patients entering the study are required to use an epilepsy/seizure diary.

This study was conducted using the International League Against Epilepsy (ILAE) 1981 classifications (Commission on Classification and Terminology of the International League Against Epilepsy, 1981), and all data and analyses were based on these classifications. Where relevant, the closest corresponding ILAE 2017 classification (Fisher et al., 2017) is also provided.

Written data consent was obtained from the patient, parent(s), or legal representative before study participation. The study protocol was reviewed and approved by an Institutional Review Board/Independent Ethics committee, per country-specific regulations.

2.2. Outcomes

This second interim analysis (data cut off: 13 April 2018) assessed effectiveness, tolerability, and HRQoL of BRV for up to 6 months. Effectiveness was assessed by BRV retention, 50 % response (≥50 % reduction from Baseline in focal seizures per 28 days), seizure freedom, median percent reduction from Baseline in focal seizure frequency per 28 days, and time to first seizure after first dose of BRV.

Where part of standard clinical practice of the participating site, HRQoL (Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 [QOLIE-31-P] Version 2) (Cramer et al., 2003), changes in cognitive function (EpiTrack) (Lutz and Helmstaedter, 2005), Clinical Global Impression of Change (CGIC), and Patient's Global Impression of Change (PGIC) were assessed.

Measured tolerability outcomes included incidence of treatment-emergent adverse events (TEAEs) and TEAEs considered drug-related by the investigator. TEAEs were defined as adverse events occurring on or after the date of first BRV administration. Adverse events included clinical adverse events and other safety relevant events such as overdose or off-label use. Adverse events were considered drug-related if they were reported as related by the investigator or if this assessment was missing.

Post hoc subgroup analyses were performed for effectiveness outcomes by number of lifetime antiepileptic drugs (AEDs) (defined as the sum of AEDs discontinued prior to study entry and concomitant AEDs taken at study entry), by historical levetiracetam (LEV) use (LEV discontinued prior to study entry), and for patients with secondarily generalised seizures (SGS) (focal to bilateral tonic-clonic seizures) during Baseline.

2.3. Statistical analyses

Because this was an observational study, all variables were summarised using descriptive statistics, and there were no inferential analyses. No sample size calculation was planned for this interim analysis. Data from patients who prematurely withdrew from the study were analysed up to the final visit attended.

The all patients documented set comprised all patients included in the study with valid data consent and for whom at least Visit 1 (Baseline) was documented. The safety set (SS) comprised all enrolled patients who received at least one dose of BRV. The full analysis set (FAS) comprised all patients in the SS who did not receive BRV before entering the study (per the protocol, patients with previous BRV use should not have been enrolled). The modified FAS (mFAS) comprised all patients in the FAS who were treated according to the approved EU Summary of Product Characteristics (SmPC) (UCB Pharma, 2018), representing the on-label use of BRV.

Patients who remained in the study and on BRV treatment for at least 3 months (>90 days) or 6 months (>180 days) after first BRV administration were classed as having 3 or 6 months retention, and percentages were based on the number of patients who had the opportunity to reach their target day of 90 or 180 days by the cut-off date, respectively. Confidence intervals (CIs) were calculated using the 2-sided exact (Clopper-Pearson) method. Seizure frequency per 28 days was calculated based on diary data for the previous 3 months, i.e., the 3 months before first BRV administration for Baseline seizure frequency and the 3 months before the 3- and 6-month visits. Percent reduction in focal seizure frequency per 28 days and 50 % response were assessed from Baseline to 3 and 6 months. Seizure freedom was assessed at 3 and 6 months, and patients were considered seizure-free if they had not discontinued the study before the visit, had no seizures before or on the visit date, and had available seizure data at the visit. Patients who discontinued the study were counted as not seizure-free and patients with missing seizure data at the visit were excluded from the analysis. The time to first seizure after first dose of BRV was analysed using

Kaplan-Meier methods.

Clinically meaningful changes from Baseline in QOLIE-31-P total scores and subscales were defined according to Borghs et al. (2012) (improvement, no change, or worsening, based on the minimally important change), and assessed at 6 months of treatment. CGIC and PGIC data were summarised as proportions of patients with improvement, no change, and worsening at 6 months. EpiTrack results were assessed as change in total score from Baseline to 6 months.

3. Results

3.1. Patient disposition and baseline characteristics

The first patient was enrolled on 16 February 2016. At the cut-off date (13 April 2018), 266 patients from five countries had attended Visit 1 (Fig. 1). Of these, 180 (67.7 %) patients had completed 3 months of observation, 127 (47.7 %) had completed 6 months, and 64 (24.1 %) had completed the study. Overall, 102 (38.3 %) patients had discontinued (Fig. 1). The most common primary reasons for discontinuation were adverse events (40 patients [15.0 %]) and lack of efficacy (39 patients [14.7 %]). A total of 261 patients had at least one dose of BRV and were included in the SS; none of them were exposed to BRV before entering the study and all were therefore included in the FAS. As these two analysis sets represent the same group of patients, SS is used to refer to the SS/FAS population throughout the Results section. Overall, 149 patients received BRV as recommended per the EU SmPC and were included in the mFAS. A total of 112 patients were excluded from the mFAS for the following reasons: daily dose <50 mg/day (28 patients), daily dose >200 mg/day (22 patients), brivaracetam not administered in equal twice-daily doses (57 patients), brivaracetam monotherapy at Baseline (two patients), violation of selection criteria (no focal seizures; two patients), and off-label use (one patient). One additional patient was listed as having a modal dose of 300 mg/day because of a partial date imputation; however, the patient was confirmed to have received doses of ≤200 mg/day by the study team, and was therefore included in the mFAS.

Patients had a mean time since epilepsy diagnosis of 23.2 years (standard deviation [SD] 14.1) and a median of five focal seizures per 28 days at Baseline (SS; Table 1). Patients had taken a mean of eight lifetime AEDs, and 80.1 % of patients were taking two or more concomitant AEDs at study entry. The most common reason for initiating BRV was lack of efficacy of previous treatment (88.1 %). Baseline demographics were similar in patients with on-label use of BRV (mFAS; Table 1). Epilepsy etiology was known in approximately half the patients (Table S1).

A total of 147/261 (56.3 %) patients had seven or more lifetime AEDs. Patients with seven or more lifetime AEDs had a longer time since diagnosis and a higher Baseline seizure frequency than those with fewer lifetime AEDs (SS; Table S2). A total of 152 (58.2 %) patients had previously received and discontinued LEV (Table 1). The most common reasons for discontinuation of LEV were insufficient efficacy (50.0 %), behavioural side effects (31.6 %), and other intolerance (11.8 %). Patients with historical LEV use had a higher Baseline seizure frequency than those without historical LEV use (median 6.00 vs 4.67 focal seizures per 28 days) and had taken a higher number of lifetime AEDs (mean 8.8 vs 6.8) (Table S3). Eighty-four patients (32.2 %) had SGS at Baseline, with a median of 1.84 SGS per 28 days (Table S4).

3.2. Exposure and dosing

The mean duration of exposure to BRV was 183.4 days (SD 140.0; median 142.0) in all patients, with a median modal dose of 100 mg/day (range 0–400 mg/day) (SS). Overall, 173/261 patients (66.3 %) initiated BRV at a dose within the recommended starting range of 50–100 mg/day (<50 mg/day: 21 [8.0 %]; >100–≤200 mg/day: 46 [17.6 %]; >200 mg/day: 4 [1.5 %]; missing: 17 [6.5 %]). At 6 months, 101/119 patients (84.9 %) took BRV at a dose within the approved dose range of 50–200 mg/day (<50 mg/day: 4 [1.5 %]; >200 mg/day: 14 [5.4 %]). During the study, 223/256 patients (87.1 %) received BRV modal doses within the recommended dose range (50–200 mg/day); however, 16 (6.3 %) received modal doses of <50 mg/day and 17 (6.6 %) received modal doses of >200 mg/day.

In patients with on-label use of BRV (mFAS), the mean duration of exposure to BRV was 188.3 days (SD 139.7; median 147.0). Patients had a median modal dose of 100 mg/day (range 50–300 mg/day).

3.3. Effectiveness: overall population

The 3- and 6-month retention rates were 189/239 (79.1 %) and 131/211 (62.1 %), respectively (SS; Fig. 2A). The Kaplan-Meier estimated median time to discontinuation of BRV or study termination was 389 days. Median percent reductions in focal seizure frequency per 28 days from Baseline to 3 and 6 months were 34.6 % (N = 139) and 53.3 % (N = 97), respectively (Fig. 2B). The 50 % responder rates for focal seizures were 65/139 (46.8 %) at 3 months and 52/97 (53.6 %) at 6 months (Fig. 2C). A total of 21/196 (10.7 %) and 15/199 (7.5 %) patients were seizure-free at 3 and 6 months of treatment, respectively (Fig. 2D). The Kaplan-Meier estimated median time to first seizure was 10 days. Similar effectiveness results were observed in the mFAS representing on-label use of BRV (Fig. 2).

3.4. Effectiveness: post hoc analyses by number of lifetime AEDs, by historical LEV use, and in SGS

Effectiveness was generally higher in patients with fewer lifetime AEDs before study entry than in those with more lifetime AEDs (SS; Fig. S1). In patients with 0–3, 4–6, and ≥7 lifetime AEDs, 6-month retention rates were 31/41 (75.6 %), 29/46 (63.0 %), and 71/124 (57.3 %), median percent reductions in focal seizure frequency per 28 days from Baseline to 6 months were 90.2 % (N = 18), 79.2 % (N = 20), and 42.4 % (N = 59), 50 % responder rates were 12/18 (66.7 %), 14/20 (70.0 %), and 26/59 (44.1 %), and seizure freedom rates were 7/37 (18.9 %), 5/43 (11.6 %), and 3/119 (2.5 %), respectively.

Retention rates at 6 months were 55/83 (66.3 %) in patients without historical LEV use and 76/128 (59.4 %) in patients with historical LEV use (SS; Fig. S2). Seizure responses at 6 months were also numerically higher in patients without historical LEV use than those with historical LEV use (median percent reduction in focal seizure

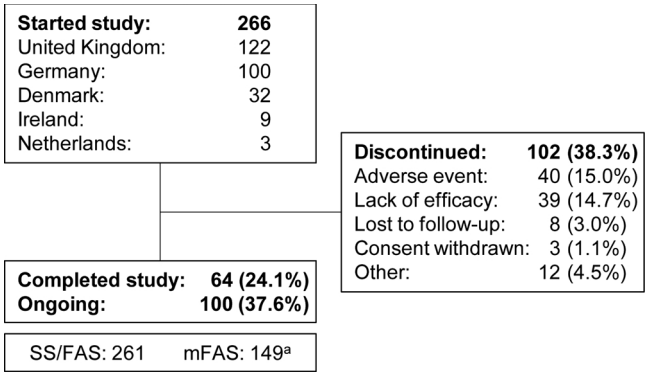

Fig. 1. Patient disposition (all patients documented set).
FAS = full analysis set; mFAS = modified full analysis set; SS = safety set.
[a]112 patients were excluded from the mFAS for the following reasons: daily dose <50 mg/day (28 patients), daily dose >200 mg/day (22 patients), brivaracetam not administered in equal twice-daily doses (57 patients), brivaracetam monotherapy at Baseline (two patients), violation of selection criteria (no focal seizures; two patients), off-label use (one patient); one additional patient was listed as having a modal dose of 300 mg/day because of a partial date imputation; however, the patient was confirmed to have received doses of ≤200 mg/day by the study team, and was therefore included in the mFAS.

Table 1
Baseline demographics and epilepsy characteristics (SS & mFAS).

	SS (N = 261)	mFAS (N = 149)
Patient demographics		
Age, mean (SD), years	42.0 (13.2)[a]	44.3 (13.6)
Female, n (%)	131 (50.2)	77 (51.7)
Epilepsy history		
Time since first diagnosis, mean (SD), years	23.2 (14.1)[b]	23.6 (15.1)[c]
Age at first diagnosis, mean (SD), years	18.6 (15.2)[b]	20.6 (15.9)[c]
Baseline seizure frequency per 28 days[d], median (Q1, Q3)		
All seizures	6.00 (3.00, 16.67)[e]	5.00 (2.33, 12.67)[f]
Focal seizures	5.00 (2.00, 16.67)[g]	4.00 (1.67, 10.00)[h]
Antiepileptic drugs		
Historical LEV use[i], n (%)	152 (58.2)	84 (56.4)
Reason for discontinuation of LEV[j,k], n (%)		
Insufficient efficacy	76 (50.0)	41 (48.8)
Behavioural side effects	48 (31.6)	26 (31.0)
Other intolerance	18 (11.8)	11 (13.1)
Other	10 (6.6)	6 (7.1)
Number of lifetime AEDs[l], mean (SD)	8.0 (4.9)	7.0 (4.2)
0–3, n (%)	52 (19.9)	38 (25.5)
4–6, n (%)	62 (23.8)	37 (24.8)
≥7, n (%)	147 (56.3)	74 (49.7)
Concomitant AEDs[m] at study entry, mean (SD)	2.4 (1.1)	2.2 (1.0)
0, n (%)	8 (3.1)	4 (2.7)[n]
1, n (%)	44 (16.9)	34 (22.8)
≥2, n (%)	209 (80.1)	111 (74.5)
Concomitant AEDs used by ≥10 % of patients at any time during the study, n (%)		
Lamotrigine	104 (39.8)	62 (41.6)
Clobazam	71 (27.2)	33 (22.1)
Levetiracetam	63 (24.1)	40 (26.8)
Valproate	62 (23.8)	32 (21.5)
Lacosamide	48 (18.4)	31 (20.8)
Carbamazepine	45 (17.2)	25 (16.8)
Zonisamide	42 (16.1)	24 (16.1)
Reason for initiation of brivaracetam[j], n (%)		
Lack of efficacy of previous treatment	230 (88.1)	132 (88.6)
Behavioural side effects to previous AED	42 (16.1)	24 (16.1)
Other intolerance to previous AED	33 (12.6)	22 (14.8)
Administer therapeutic dose without titration	8 (3.1)	5 (3.4)
Other	10 (3.8)	7 (4.7)
Missing	1 (0.4)	0

AED = antiepileptic drug; LEV = levetiracetam; mFAS = modified full analysis set; Q1 = first quartile; Q3 = third quartile; SD = standard deviation; SS = safety set; VNS = vagus nerve stimulation.
[a]N = 260; [b]N = 256; [c]N = 147; [d]Based on previous 3 months; [e]N = 234; [f]N = 131; [g]N = 229; [h]N = 126; [i]AEDs discontinued prior to study entry; [j]More than one reason could be given; [k]Percentage is based on the number of patients with historical LEV use; [l]Lifetime AEDs were defined as a sum of the historical AEDs and concomitant AEDs taken at study entry (including VNS and LEV counted only once); [m]VNS was counted as an AED; [n]These patients took concomitant AEDs during the study, but were counted as having no concomitant AEDs at study entry because of date imputation.

frequency per 28 days from Baseline: 75.7 % [N = 38] vs 44.9 % [N = 59]; 50 % responder rate: 24/38 [63.2 %] vs 28/59 [47.5 %]; seizure freedom: 9/80 [11.3 %] vs 6/119 [5.0 %]).

In patients with SGS at Baseline, the 6-month retention rate was 41/70 (58.6 %), median percent reduction in SGS frequency per 28 days from Baseline to 6 months was 75.9 % (N = 34), 23/34 (67.6 %) patients had a 50 % reduction in SGS, and 13/71 (18.3 %) patients were free from SGS at 6 months of treatment (SS; Fig. S3).

Similar effectiveness results were observed in patients with on-label use of BRV (mFAS; Figs. S1–S3).

3.5. Health-related quality of life

In this study, 44.2 % of patients reported an improvement and 15.4 % reported a worsening in QOLIE-31-P total score from Baseline to 6 months of treatment (SS; N = 52; Fig. 3). In physicians' responses to the CGIC questionnaires at 6 months of treatment (N = 68), 66.2 % of patients had an overall improvement and 10.3 % had a worsening from Baseline. Similar results were seen in patients' responses to the PGIC at 6 months (N = 60; 56.7 % improvement, 20.0 % worsening).

The EpiTrack tool was used to assess changes in cognitive function. The mean EpiTrack total score was 31.2 (SD 5.9) at Baseline and 32.4 (SD 6.1) at 6 months (SS; N = 33). No major changes were observed in the EpiTrack total score at 6 months, with a median change from Baseline of 0.0 (Q1 to Q3: −1.0 to 3.0; N = 33).

3.6. Safety and tolerability

Overall, 133 (51.0 %) patients reported at least one TEAE, and 90 (34.5 %) had TEAEs considered drug-related by the investigator (SS, Table 2). The most common drug-related TEAEs (reported in ≥5% of patients) were drug ineffective (7.7 %; reported terms included: lack of efficacy, insufficient efficacy, discontinuation due to lack of efficacy, and no better seizure control), seizure (6.5 %), and fatigue (6.1 %). Serious drug-related TEAEs reported by at least three patients were seizure (11 [4.2 %]) and suicidal ideation (3 [1.1 %]). Discontinuations of BRV due to drug-related TEAEs were reported by 59 patients (22.6 %), most commonly (≥5%) drug ineffective (19 patients [7.3 %]) and seizure (14 [5.4 %]). One patient died after 28 days of treatment (unexpected death). This death was not considered related to BRV by the investigator. The incidences of drug-related TEAEs were similar in patients with on-label use of BRV (mFAS; Table 2).

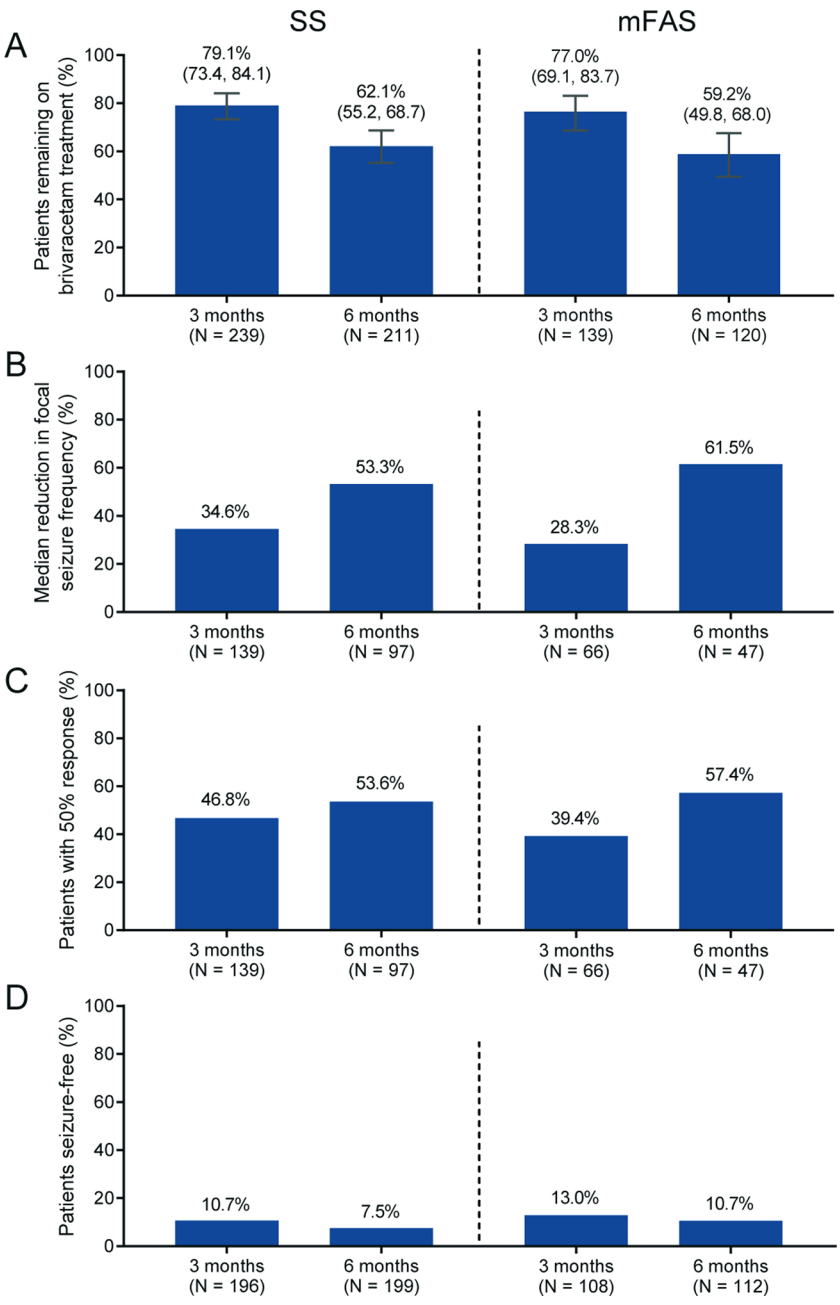

Fig. 2. Effectiveness outcomes at 3 and 6 months of treatment (SS & mFAS).
CI = confidence interval; mFAS = modified full analysis set; SS = safety set.
(A) Retention rates. Error bars represent 95 % CIs. Retention is defined as remaining in the study and being on brivaracetam treatment at least 3 months (>90 days) or at least 6 months (>180 days) after first brivaracetam administration. Percentages are based on the number of patients with data at the respective visit. (B) Median percent reduction in focal seizure frequency per 28 days from Baseline based on the number of patients with data at the respective visit. (C) 50 % responder rates. Percentages are based on the number of patients with data at the respective visit. (D) Seizure freedom. Seizure freedom was defined as having no seizures recorded in the study on or before the visit date, having not discontinued before the visit, and having available seizure data at the visit.

4. Discussion

The interim results of this prospective, observational study indicate that adjunctive BRV is effective and well tolerated in drug-resistant patients (≥16 years) with focal seizures when used in clinical practice across five European countries (United Kingdom, Germany, Denmark, Ireland, and Netherlands).

In this study, 3-month (79.1 %) and 6-month retention rates (62.1 %) for adjunctive BRV were comparable with those observed in several retrospective non-interventional studies of BRV (3 months: range 79.4–90.8 %; 6 months: range 51.5–80.2 %) (Steinhoff et al., 2017a; Steinig et al., 2017; Villanueva et al., 2019). Seizure assessments at 3 months showed numerically higher 50 % responder (46.8 % vs 21.9–38.9 %) and seizure freedom rates (10.7 % vs 0–5.2 %) than observed in three randomised, double-blind, placebo-controlled, pivotal Phase III trials of adjunctive BRV (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014). Median percent reduction in focal seizure frequency from Baseline were at the upper end of the range observed in the pivotal trials (34.6 % vs 20.0–37.2 %). This might be due to differences in dosing. In the pivotal trials, patients were randomised to fixed doses (5/20/50 mg/day, 100/200 mg/day, 20/50/100 mg/day) (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014), whereas in this non-interventional study reflecting real life medical practice, doses were determined by the treating physician, and individualised to the needs of a specific patient. In this interim analysis, 66.3 % of patients initiated BRV at a dose within the recommended starting range of 50–100 mg/day (UCB Pharma, 2018) and received modal doses of 50–200 mg/day during the study. At 6 months, 53.6 % of patients were 50 % responders and 7.5 % were seizure-free, with a median percent reduction in focal seizure frequency from Baseline of 53.3 %. Similar 3- and 6-month 50 % responder (3 months: 41.2–42.4 %; 6 months: 27.8–40.5 %) and seizure freedom rates (3 months: 14.9–19.1 %; 6 months: 6.9–17.2 %) were reported in other non-interventional studies of BRV (Steinhoff et al., 2017a; Steinig et al., 2017; Villanueva et al., 2019).

As in the pivotal trials (Biton et al., 2014; Klein et al., 2015; Ryvlin et al., 2014) and retrospective studies of BRV (Steinhoff et al., 2017a;

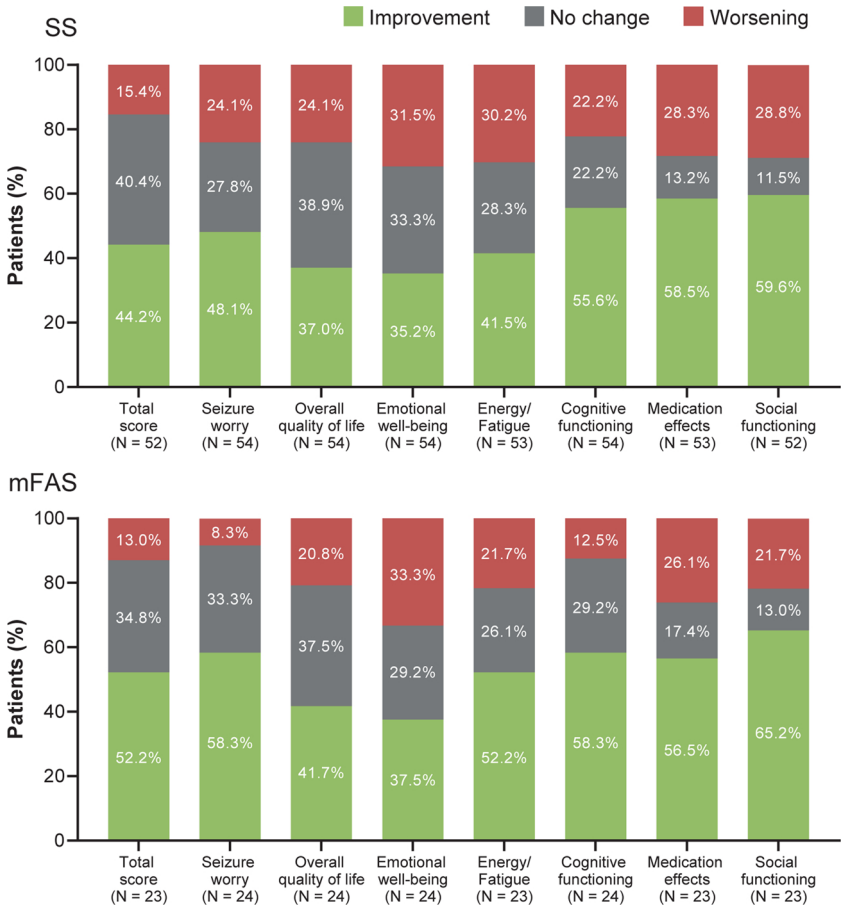

Fig. 3. Clinically meaningful change from Baseline to 6 months of treatment in QOLIE-31-P (SS & mFAS).
mFAS = modified full analysis set; QOLIE-31-P = Patient Weighted Quality of Life in Epilepsy Inventory-Form 31; SS = safety set.

Steinig et al., 2017; Villanueva et al., 2019), the Baseline characteristics in this study indicated that the patient population was highly drug-resistant. Effectiveness data should be viewed in that context. Enrolled patients had a long history of epilepsy, with a mean time since diagnosis of 23.2 years. Patients had a median of five focal seizures per 28 days at Baseline, although 80.1 % were receiving treatment with two or more concomitant AEDs. Overall, 56.3 % of patients had seven or more lifetime AEDs, and 88.1 % initiated BRV because of a lack of efficacy of previous AED treatment.

Post hoc subgroup analyses showed numerically better effectiveness in patients with 0–3 or 4–6 lifetime AEDs than those with seven or more lifetime AEDs. This is not unexpected as patients with a high number of lifetime AEDs are more likely to be drug-resistant (Schiller, 2009; Schiller and Najjar, 2008). In line with this, patients with seven or more lifetime AEDs had a longer time since diagnosis and a higher Baseline seizure frequency than those with fewer lifetime AEDs. Consistent with our results, patients with fewer lifetime AEDs were more likely to achieve seizure freedom in a retrospective non-interventional study of BRV (Villanueva et al., 2019). Furthermore, in a post hoc analysis of a randomized, double-blind trial of adjunctive BRV, numerically higher 75 % responder rates were seen in patients with fewer lifetime AEDs (Klein et al., 2019).

Effectiveness of BRV in patients with prior LEV use has been demonstrated in retrospective studies in clinical practice (Hirsch et al., 2018; Steinig et al., 2017). In the current study, BRV was effective regardless of whether patients had historical LEV use; however, responder rates and median percent reduction of focal seizures were numerically lower in patients with historical LEV use. The subgroup of patients with historical LEV use had a higher Baseline seizure frequency and a higher number of lifetime AEDs than those without historical LEV use. These factors may have contributed to the observed results.

Similar effectiveness results were seen in other studies comparing LEV-naive patients with those previously exposed to LEV. In a retrospective non-interventional study of BRV in Spain, more LEV-naive patients than those with previous LEV exposure were seizure-free at 3 (26.0 % vs 12.0 %), 6 (23.6 % vs 11.1 %), and 12 months of treatment (17.9 % vs 13.4 %) (Villanueva et al., 2019). In a retrospective study in Germany, higher 6-month retention rates were seen in patients without previous LEV use than in the overall population (57 % vs 51.5 %) (Steinhoff et al., 2017a). In a post hoc analysis of pooled data from the pivotal trials of BRV, 50 % responder rates were higher in LEV-naive patients (44.3 %) than patients with previous LEV exposure (30.0 %) (Asadi-Pooya et al., 2017). It should be noted that similar results were observed in patients with prior exposure to carbamazepine, lamotrigine, and topiramate (Asadi-Pooya et al., 2017). Similar to our study, the subgroups of patients with previous exposure to LEV, carbamazepine, lamotrigine, and topiramate had a higher number of previously failed AEDs at Baseline, indicating that they were more difficult to treat than patients who had never taken these particular AEDs. Nonetheless, BRV was efficacious even in patients who had been previously exposed to and failed other AEDs including LEV (Asadi-Pooya et al., 2017). A subsequent post hoc analysis of one of the pivotal trials and the corresponding open-label extension demonstrated similar long-term retention rates on adjunctive BRV and similar reasons for BRV discontinuation in patients with previous LEV, carbamazepine, lamotrigine, and topiramate, indicating that previous treatment failure with LEV does not preclude the use of BRV (Martin et al., 2019).

A total of 32.2 % of patients had SGS at Baseline. In this subgroup, retention rates were similar to those observed in the overall population, while responder rates and seizure freedom rates for SGS were

Table 2
Summary of TEAEs and drug-related TEAEs (SS & mFAS).

Patients, n (%)	SS (N = 261)	mFAS (N = 149)
Any TEAEs	133 (51.0)	61 (40.9)
Serious TEAEs	34 (13.0)	16 (10.7)
Discontinuations due to TEAEs	72 (27.6)	39 (26.2)
Deaths	1 (0.4)	0
Most common TEAEs[a] (≥5% of patients in the SS)		
Drug ineffective[b]	43 (16.5)	20 (13.4)
Off-label use[c]	38 (14.6)	1 (0.7)[d]
Seizure[e]	21 (8.0)	10 (6.7)
Overdose[f]	20 (7.7)	0
Fatigue	17 (6.5)	7 (4.7)
Drug-related TEAEs	90 (34.5)	47 (31.5)
Serious drug-related TEAEs	21 (8.0)	12 (8.1)
Discontinuations due to drug-related TEAEs	59 (22.6)	34 (22.8)
Most common drug-related TEAEs[a] (≥1% of patients in the SS)		
Drug ineffective[b]	20 (7.7)	10 (6.7)
Seizure[e]	17 (6.5)	10 (6.7)
Fatigue	16 (6.1)	7 (4.7)
Dizziness	10 (3.8)	7 (4.7)
Adverse event[g]	9 (3.4)	7 (4.7)
Headache	7 (2.7)	3 (2.0)
Irritability	7 (2.7)	2 (1.3)
Unevaluable event[h]	6 (2.3)	5 (3.4)
Depressed mood	6 (2.3)	3 (2.0)
Aggression	5 (1.9)	2 (1.3)
Somnolence	4 (1.5)	2 (1.3)
Sedation	3 (1.1)	3 (2.0)
Abnormal behaviour	3 (1.1)	2 (1.3)
Suicidal ideation	3 (1.1)	2 (1.3)
Diplopia	3 (1.1)	1 (0.7)
Disturbance in attention	3 (1.1)	1 (0.7)
Mood altered	3 (1.1)	1 (0.7)
Condition aggravated[i]	3 (1.1)	0

TEAEs were listed in accordance with the EMA requirements for safety reporting.
CGIC = Clinical Global Impression of Change; EMA = European Medicines Agency; MedDRA = Medical Dictionary for Regulatory Activities; mFAS = modified full analysis set; SS = safety set; SmPC = Summary of Product Characteristics; TEAE = treatment-emergent adverse event.
[a]Preferred Term (MedDRA, Version 21.0); [b]Reported terms included: lack of efficacy, insufficient efficacy, discontinuation due to lack of efficacy, and no better seizure control; [c]Reported for situations where brivaracetam is intentionally used for a medical purpose not in accordance with the SmPC; [d]Patient started brivaracetam at a dose of 75 mg twice daily; [e]Reported terms included: continuous seizures, discontinuation due to seizure worsening, hospitalisation due to seizures, increased seizure frequency, seizure, seizures (multiple episodes), and worsening of seizures; [f]Reported for excessive dosing, independently of whether there is an adverse event associated; [g]Reported terms included: adverse event (not otherwise specified), much worse / CGIC, and study dropout due to adverse event; [h]Reported terms included: other intolerance, remember dreams at night, and increase of attack; [i]Reported terms: CGIC much worse.

numerically higher than those for all focal seizure types in the overall population, indicating that BRV may be effective in controlling SGS. These results should be interpreted with caution due to the small number of patients with SGS. In a retrospective study in Germany, similar responder rates and seizure freedom were seen at 6 months in all patients with epilepsy (N = 192; all seizure types assessed) and the subgroup of patients with generalised tonic-clonic seizures (N = 92; generalised tonic-clonic seizures assessed) (Steinig et al., 2017). A post hoc analysis of pooled data from the three pivotal trials found that adjunctive BRV was effective in reducing the frequency of SGS in patients with drug-resistant seizures (Moseley et al., 2016).

In the overall population, a numerically higher proportion of patients had an improvement than a worsening in HRQoL (QOLIE-31-P) total score and individual domains, CGIC, and PGIC, and BRV did not affect cognitive profile as assessed by EpiTrack and the QOLIE-31-P subdomain 'cognitive functioning'. BRV displayed a tolerability profile consistent with its known tolerability profile. At the time of this interim analysis, 59/261 (22.6 %) patients had discontinued due to drug-related TEAEs. However, it should be noted that the most common drug-related TEAEs leading to discontinuation were drug ineffective (19 patients) and seizure (14 patients). These events were classified as TEAEs in accordance with the European Medicines Agency requirements for safety reporting.

A potential limitation of the multinational study design is the heterogeneity of data because of differences in clinical practice between countries. The interim data reported here should be interpreted with caution as they represent a snapshot of the study, with ~50 % of planned number of patients recruited at the cut-off date. Interpretation of some outcome measures is limited by the low patient numbers, as some of the enrolled patients had not yet completed 6 months of treatment at the cut-off date. In addition, some parameters had not been entered into the database at the time of analyses, leading to some missing data, even for patients that completed 6 months of treatment. All outcomes in this observational, non-interventional study were analysed using descriptive statistics only. Interpretation of the subgroup analyses is limited by their post hoc nature and low patient numbers in some of the subgroups.

5. Conclusions

In this 6-month, second interim analysis of a prospective, observational study, adjunctive BRV showed effectiveness in drug-resistant patients when used in clinical practice in five European countries. BRV was well tolerated and the reported adverse events were consistent with the known tolerability profile reported in pivotal trials. Post hoc analyses showed numerically better effectiveness in subgroups of patients with 0–3 or 4–6 lifetime AEDs prior to study entry than in those with seven or more lifetime AEDs, who likely represent a more drug-resistant patient population. A subgroup analysis of patients with SGS at Baseline indicated that BRV may also be effective in controlling SGS.

Declaration of Competing Interest

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Research data for this article

Data from non-interventional studies are outside of UCB Pharma's data sharing policy.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.eplepsyres.2020.106329.

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