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BRIVEST: A 'real-world' observational, single-centre study investigating the efficacy, safety and tolerability of Brivaracetam

Sophie Naddell [a], Megan Manuel [a], Rebecca Cavill [a], Paul White [b] and Katarzyna Sieradzan [a]

[a] Department of Neurology, Southmead Hospital, North Bristol NHS Trust, United Kingdom; [2] Department of Data Science and Mathematics, University of the West of England, Bristol, United Kingdom

Corresponding Author: Sophie Naddell, *sophie.naddell@nbt.nhs.uk*

Abstract

Objective: Via measures of efficacy, tolerability and safety, this partially prospective open-label, single-centre study assessed the overall effectiveness of brivaracetam (BRV) for the treatment of epilepsy in the context of 'real-world' clinical practice.

Methods: Unselected consecutive patients were recruited and stratified into 3 cohorts with either fully prospective, fully retrospective or mixed data collection, dependent on whether their BRV prescriptions were historical, current or pending. Prospective data were obtained at baseline, 3 and 6 months, and at 6-month intervals thereafter, from patient interviews and seizure diaries, and retrospective data from medical records. Efficacy variables were derived from seizure-related changes, and tolerability and safety variables from reported treatment-emergent adverse events (TEAEs), BRV withdrawal, and changes to questionnaire scores. Additionally, we investigated treatment outcomes for those with previous levetiracetam (LEV) use, history of psychiatric comorbidity, learning disability, and of older age.

Results: One hundred and nine patients (58.7% female, mean age 42 years, range: 18 to 72) were included, 59 with prospective follow-up for minimum 6 (47 patients, excluding those who withdrew) and maximum 24 months (2 patients). Of the full cohort 87.2% had drug-resistant epilepsy.
Retention: At study end, median treatment duration was 384 days (range: 6 to 1514 days), and BRV retention was 68.8%. Kaplan-Meier survival functions predicted retention rates of 74.0% and 70.0% at 6 and 12 months respectively.
Efficacy: At last follow-up, there was a ≥ 50% responder rate of 30.8%, with 12.1% seizure-free. Seizure frequency categories improved in 31.4% patients, remained the same in 44.2% and worsened in 24.4%. Monthly tonic-clonic seizure frequency had significantly decreased, and of those reporting these seizures, 58.3% showed reductions and 25.0% showed complete tonic-clonic seizure freedom.
Tolerability: 91.7% patients reported at least 1 TEAE, with fatigue (30.3%), irritability (29.4%) and depression/low mood (28.4%) the most common. Only 58.4% of all TEAEs were persistent. BRV discontinuation due to side effects occurred in 27.5% of the cohort. Depression and anxiety scores remained stable over time, and quality of life scores improved.
Subgroups: Measures of BRV efficacy and tolerability did not differ according to previous LEV exposure. Tolerability profiles of those with learning disabilities, histories of psychiatric comorbidities, and of older age did not greatly differ from the rest of the cohort. Of note, specific history of depression predicted the reporting of suicidal ideation.

Conclusion: The BRIVEST study provides real-world evidence on the effectiveness of BRV, suggesting that neither drug-resistant epilepsy nor previous LEV failure should preclude its use. Furthermore, BRV appears to be well-tolerated, even among those from vulnerable patient populations.

Keywords: epilepsy; brivaracetam; prospective; real-world study.

1 INTRODUCTION

With over 70 million diagnoses worldwide, epilepsy is one of the most prevalent of the serious neurological diseases and a major source of morbidity, mortality and healthcare cost [1,2]. Despite a growing catalogue of anti-seizure medications (ASMs), around one third of patients are resistant to treatment [3], and many experience adverse side effects [4]. Both improved ASM efficacy and tolerability are necessary for optimal concordance and clinical outcomes. Brivaracetam (Briviact®; BRV), a novel member of the racetam class and an analogue of levetiracetam (LEV), is among the newest 'third generation' ASMs, and its use has increased globally since its original licensing in 2016 [5]. It is currently licensed for adjunctive therapy for focal epilepsy in Australia for patients ≥ 4 years of age [6], in Europe for patients ≥ 2 years of age [7], and in the USA for adjunctive and monotherapy for patients ≥1 month of age [8]. Across the last decade, various randomised-controlled trials (RCTs) [9–14], post-marketing studies and meta-analyses have shown BRV to be effective and well-tolerated when compared to various other ASMs, in the treatment of focal seizures with and without secondary generalisation [3,15]. The present study adds to the growing body of "real-word" data concerning the use of BRV in routine clinical practice.

1.1 Mode of Action

Like LEV, BRV is a ligand of synaptic vesicle protein 2A (SV2A) [16], a presynaptic membrane glycoprotein widely expressed in the brain and implicated in vesicle trafficking and exocytosis - processes which are vital for neurotransmission [17]. SV2A appears to play an important role in epileptogenesis, with mice deficient in SV2A demonstrating increased propensity for seizures [18]. How exactly ligand binding to SV2A reduces seizure susceptibility is not fully elucidated, but it is thought that binding of both LEV and BRV alters protein conformation and modulates presynaptic neurotransmitter release, leading to suppression of neuronal hyperexcitability [19]. In terms of their pharmacodynamic profiles, BRV has a 15- to 30- fold higher binding affinity to SV2A than LEV [20–22], significantly faster human brain penetration and SV2A occupancy [23], and greater binding selectivity [24]. Unlike LEV, BRV does not show any modulatory activity at inhibitory (glycine, GABA) or excitatory (glutamate) post-synaptic receptors [25], a characteristic which may underpin its supposedly favourable psychotropic effects [26–28].

1.2 Efficacy & Tolerability

Prior to its licensing, 6 regulatory phase IIb and Phase III double-blind, randomised, placebo-controlled studies comprising 2399 patients demonstrated the superior seizure control over placebo, and reasonable tolerability of BRV [9–14; see 3,15, and 29 for overviews]. Several post-hoc meta-analyses [30–33], and long-term follow-up (LTFU) studies [5,34,35] similarly concluded that BRV is effective and generally well tolerated when administered long-term. Although encouraging, these data have been derived under controlled settings (e.g. dosing schedule, co-medication) and set inclusion and exclusion criteria (e.g. exclusion of those with certain medical and psychiatric comorbidities [10,34], those with histories of suicidal ideation or attempt [5],or those below certain baseline seizure frequency thresholds). This limits the direct transferability of findings to the 'real-world' practical application of BRV. A growing but still limited number of prospective and observational 'real-world' studies have used less stringent eligibility criteria to explore BRV treatment outcomes in everyday clinical settings within more heterogeneous patient populations. Whilst these have generally corroborated earlier conclusions, exact figures relating to seizure reduction and treatment-emergent adverse events have varied significantly, likely due to differences in study methodology. Among the retrospective 'real-world' studies we identified, responder rates (proportion of those with ≥50% seizure reduction from baseline) ranged from 21.0% to 71.0%, seizure freedom rates from 7% to 36%, treatment-emergent adverse event (TEAE) rates from 17.0% to 39.8%, and BRV withdrawal rates from 8.9% to 28.9% [28,36–41]. The most commonly reported side effects included dizziness, irritability, somnolence, fatigue, anxiety and depression. Retrospective study designs, however, present the risk of inaccurate seizure capture and under-detection of TEAEs. Real-world *prospective* studies concerning BRV are very limited, but of the three we identified, data were, as expected, slightly less favourable with ≥50% responder rates 28.0% - 38.0%, seizure freedom rates 7.0% - 21.3%, TEAE rates 37.0% - 78.0% and BRV withdrawal rates 34.3% - 48.5% [42–44]. Dizziness, somnolence, depression and aggression were among the most frequent side effects.

1.3 Special populations

Of interest from the real-world data concerning BRV is its effectiveness in specific patient groups for whom sufficient clinical data are still limited, including children and older adults, those with previous exposure to LEV, those with comorbid learning disabilities (including developmental and epileptic encephalopathy (DEE)), and those with histories of psychiatric comorbidities.

One major attraction of BRV is the possibility of superior tolerability with equivalent efficacy compared to LEV. Evidence of both similar [43] and superior efficacy [39] suggests that previous LEV failure should not preclude trialling BRV. In terms of tolerability, the literature points overwhelmingly to reduced incidence of TEAEs, particularly psychiatric adverse effects (PAEs) associated with LEV treatment among those switching to BRV treatment [28,36,37,43–47,48]. Several studies have, however, reported reduced seizure control among those with previous LEV exposure compared to those without [31,35,36,39]. This might be explained, at least in part, by a more refractory epilepsy profile among those with histories of failed LEV treatment [35,39,49].

Psychiatric comorbidity is disproportionately high among people with epilepsy (PWE) [1]. A population-based study found one third of epilepsy patients had a diagnosis of anxiety or depressive disorder, a rate twice as high as in the general population [50], and a recent meta-analysis reported suicidal ideation, suicide attempts and death by suicide to be significantly higher in PWE compared to the general population [51]. Considering that pre-existing psychiatric comorbidity is a primary risk factor for development of PAEs with ASM treatment [52], it is important to better characterise the psychiatric profile of BRV, both in terms of emergence of PAEs in healthy patients, and responses among those already vulnerable. This is especially important given the shared mechanisms of BRV and LEV, and the recognised associations between LEV treatment and emergence of PAEs [53].

Despite the higher prevalence of epilepsy among those with learning disabilities (LD) compared with the general population [54], these patients are often excluded from clinical trials. The small number of studies investigating BRV outcomes among this subgroup to date [36,38,43,55,56] have found BRV to be generally well-tolerated, although negative behavioural changes have been noted [43, 55]. Suitable treatment options for those of older age also merit special attention, with epilepsy being the third most common neurological disorder among older adults after stroke and dementia [57]. Age-related changes to pharmacokinetics of ASMs, alongside often complex comorbidities and co-medications, may increase susceptibility to adverse effects [57], and as such further research on the effects of BRV in older adults is necessary.

1.4 Present Study

Here, we describe the findings of a single-centre observational study of the effectiveness of BRV for adults in everyday 'real-world' clinical practice, in terms of its efficacy, tolerability and safety. Psychiatric and behavioural side effects, and their impacts on mental wellbeing and quality of life, were of special interest. The absence of strict inclusion and exclusion criteria allowed for a truly consecutive, unselected, and thus more heterogeneous study population, including subgroups of patients with histories of psychiatric comorbidities, comorbid learning difficulties, those of older age and those previously exposed to LEV. We were able to adopt a prospective study design with one subset of our cohort, enabling more precise and 'real-time' recording of data concerning seizure frequency and TEAEs.

2 METHODS

BRIVEST (Brivaracetam: Efficacy, Safety and Tolerability) was an open-label, single-centre observational study conducted at North Bristol NHS Trust's Epilepsy Service, a secondary care specialist centre for epilepsy in Bristol, and a tertiary centre for the South West of England. The study protocol, amendments, and materials were approved by the relevant authorising bodies. Data collection, storage and management were compliant with Good Clinical Practice and in accordance with the Declaration of Helsinki.

2.1 Patient population

Study recruitment took place between September 2018 and April 2020, and patient follow-up continued until October 2020. Unselected consecutive patients with a current, past or pending BRV prescription were

identified from pharmacy prescription records spanning May 2016 (when BRV became available on the North Bristol Trust formulary) until April 2020 (when recruitment closed). Exclusion criteria were kept to a minimum: those for whom reliable seizure diaries could not be kept, those unable to attend study appointments, and those aged < 18 years old) (see *Appendix A)*. Of the 242 patients identified as eligible, 109 (45.0%) were successfully recruited and followed up, with minimum follow-up of 3 months from start of BRV treatment (this also captured cases of BRV withdrawal before this point), and maximum of 24 months. Although BRV is currently licenced as adjunctive therapy for focal-onset seizures in the UK, we included those on BRV monotherapy or with generalised epilepsies to reflect the real-world off-label prescribing of BRV [41,58]. Whenever possible, follow-up was prospective from the start of BRV exposure, but we also included patients who had commenced BRV treatment prior to study start.

2.2 Design & Materials

The study population was stratified into 3 cohorts. See *Figure 1* for study timeline and recruitment/withdrawal activities. In order to reduce data bias that favoured those with successful BRV experiences, we included patients who had withdrawn BRV treatment prior to study commencement; they formed the 'true retrospective' (TR) cohort (N=15), and were not required to provide informed consent, due to use of anonymised retrospective data from routine clinical care. Those receiving BRV treatment at the time of the study start were offered participation and formed a 'true prospective' (TP) (N=59) and a mixed 'retrospective-prospective' (RP) cohorts (N=35). The RP cohort comprised those who were first contacted more than 7 months after starting treatment with BRV (with a +/- 1 week flexibility window to accommodate for arranging appointments). Informed consent was obtained from all patients in the TP and RP cohorts, and for those unable to give their informed consent, consenting involved their personal and professional consultees and/or legal representatives according to the process approved by the Ethics Committee.

For the TR cohort, data on patient demographics, efficacy and tolerability of BRV, and reasons for withdrawal were collected from neurology clinic records. For the TP and RP cohorts, patient interviews determined patient demographics, previous ASM history, real-time seizure frequency, BRV dosage, and concomitant ASMs (all corroborated by neurology clinic notes wherever possible). As measures of quality of life, the Beck Anxiety Inventory (BAI), Beck's Depression Inventory (BDI), and Quality of Life in Epilepsy (QOLIE-31-P) (Version 2) questionnaires were administered. The BAI has been approved for use among those with epilepsy [59], and the BDI and QOLIE-31-P have shown good validity in epilepsy [60–62].

As a baseline, seizure frequency and seizure types occurring in the 3 months prior to initiation of BRV treatment were carefully estimated through an amalgam of self-reporting and clinic notes. Upon first meeting, patients were asked to keep seizure diaries throughout the course of the study. Follow-up data were collected at 3, 6, 12, 18 and, in 2 cases, 24 months from BRV commencement for the TP cohort, and at 6 and 12 months after the first study meeting for the RP cohort. As such, study 'timepoints' occurred at varying dates depending on patients' own prescription timelines, as did the duration of patients' prospective follow-up periods.

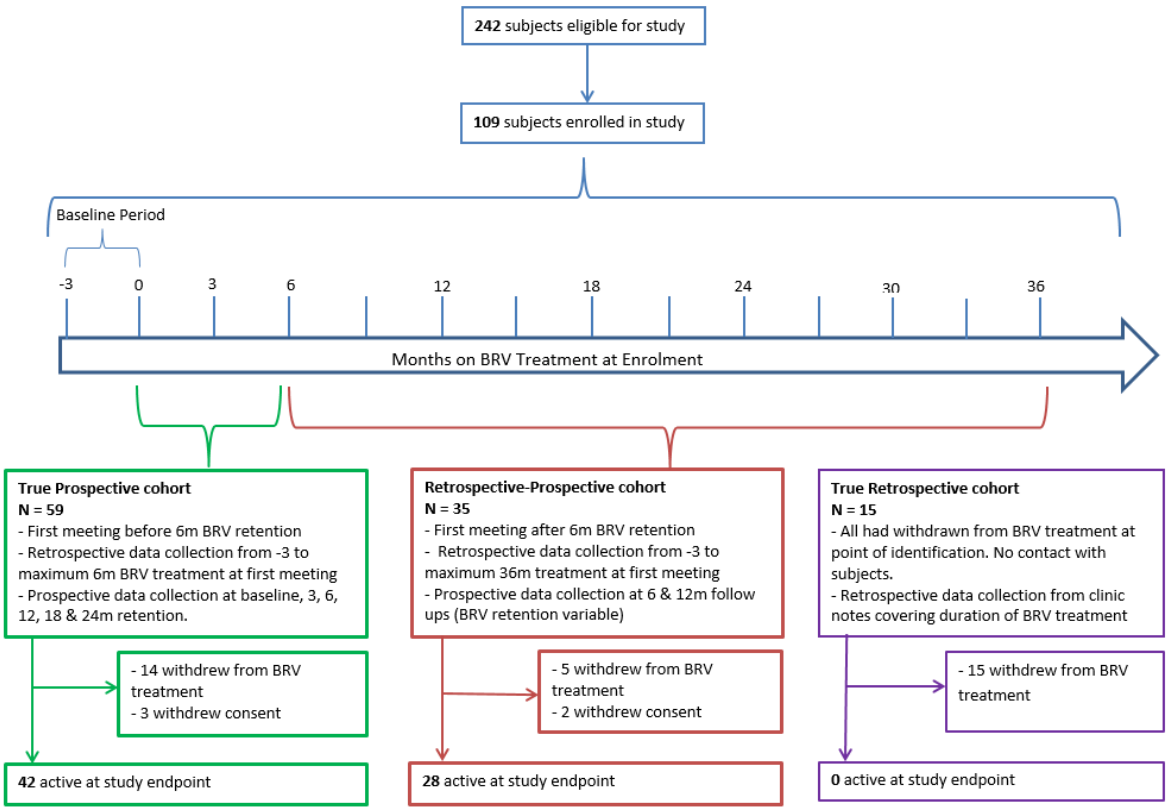

FIGURE 1. Visualisation of patient recruitment, stratification of population into 3 study cohorts, and study retention by cohort.

2.3 Outcome Measures

2.3.1 Efficacy

Due to predominantly qualitative retrospective data, we excluded the TR cohort from all analyses of BRV efficacy other than those relating to seizure freedom, which could be captured accurately. The primary efficacy variable, 'responder rate', was based on percentage seizure reduction from baseline at a given follow-up, and categorised as follows: 100% (seizure freedom), ≥ 50% (clinically significant improvement- 'responder') and ≥ 25% to <50% (marginal improvement). Those with <25% reduction or any increase in seizures from baseline were considered non-responders to BRV treatment, as were those who withdrew BRV treatment (in line with others [42], this included those who withdrew treatment due to tolerability reasons). Like in similar studies [36], seizure freedom was defined here as experiencing no seizures of any kind since the previous study time-point. Responder rates were calculated at 3, 6, 12, 18 and, in 2 cases, 24 months retention for the TP cohort, and at 'last available follow-up' for the TP and RP cohorts combined. Those who withdrew consent, had unavailable data, or had not yet completed a given follow-up were excluded from analyses, but to avoid biasing data towards efficacious BRV treatment, those who had withdrawn BRV were included in these analyses. Specifically, and in line with others [38], they were included in the follow-up analysis corresponding to the period during which they withdrew (e.g. 12-month follow-up for 6-12 months).

We also examined changes among the TP cohort in mean average monthly seizure frequency from baseline (the 3 months preceding BRV commencement) to the following study time points: 3m (0-3 months), 6m (3-6 months), 12m (6-12 months) and 18m (12-18 months). Data were insufficient for inclusion of 24m (18-24 months). The RP cohort was not large enough to consider changes in monthly seizure frequency from baseline to 6 and 12m follow-ups, however data from the TP and RP cohorts were pooled for analyses at last available prospective follow-up. In all cases, separate analyses were performed for focal aware seizures, focal impaired awareness seizures, tonic-clonic seizures (both focal and generalised), and all seizure types (the former two

included only those patients with focal or combined onset epilepsy, and the latter two included those with generalised onset epilepsy too). Classifications here were in line with the latest ILAE commission for classification and terminology [63].

As an additional analysis of efficacy for the TP and RP cohorts, we included changes to seizure frequency categories from baseline to last available follow-up in order to capture clinically meaningful change. Seizure frequency categories were defined, in line with others [38], as follows: 1 = seizure-free, 2 = ≥ 1 seizure per year but < 1 seizure per month, 3 = ≥ 1 seizure per month but < 1 seizure per week, 4 = ≥ 1 seizure per week but < 1 seizure per day, and 5 = ≥ 1 seizure per day.

2.3.2 Tolerability and Safety

Primary tolerability and safety variables included the overall incidences of TEAEs and TEAEs specifically psychiatric in nature (psychiatric adverse events - 'PAEs') and rates of withdrawal due to TEAEs. Data from all 3 cohorts were included. TEAEs were assessed via open-ended questions regarding new or exacerbated symptoms that patients felt may be related to BRV treatment. Any reporting of additional symptoms prompted by the subsequent completion of the mood questionnaires were not considered potential side effects, unless explicitly described as such at the time by patients. In addition, changes in QOLIE-31-P, BDI and BAI questionnaire scores from baseline were analysed, at 3, 6, 12, and 18 months retention for the TP cohort (data insufficient at 24 months), and at 6 and 12-month follow up for the RP cohort.

2.3.3 Subgroups

TEAE rates were compared in those with and without previous LEV exposure, with and without learning disabilities, with and without histories of psychiatric comorbidities, and those over and under 65 years of age. Additionally, in light of the mixed evidence base concerning the effects of previous LEV exposure on BRV efficacy, responder rates and changes to monthly seizure frequency were compared in those who were LEV-exposed vs LEV-naïve.

2.4 Statistical Methods

Data were analysed using IBM SPSS Statistics, version 26.0 (IBM Corp., Armonk, NY, USA). No sample size calculation was performed, but the number of patients recruited (n=109) reflected similar studies (e.g. 42,44). Due to the observational open-label design, descriptive statistics were often used including minimum and maximum values, lower quartile (Q1), median, upper quartile (Q3), maximum, interquartile range (IQR) and the mean and standard deviation (SD). BRV retention was modelled with Kaplan–Meier survival curves. The Wilcoxon signed-rank test was employed for analyses of changes to seizure frequency categories, and effect sizes, 'r', were calculated, with $r = z/\sqrt{N}$. The Mann-Whitney U test was used for i) comparisons of changes in seizure frequencies between the LEV-exposed and LEV-naive subgroups and ii) explorations of relationships between response to BRV and the number of past and concomitant ASMs. To compare subgroup demographics, Fisher's exact test and the Mann-Whitney U test were used for categorical and nonparametric scale data, respectively. Fisher's exact test was employed for subgroup TEAE rate comparisons in the case of 2x2 contingency tables, and its extension, the Fisher-Freeman-Halton test, was used for higher-order contingency tables. Here, the Cochran-Mantel-Haenszel test delivered odds ratio estimates. Changes in questionnaire scores over time were examined using a linear mixed model for longitudinal data. For all tests, statistical significance was set at the 5% level (two-sided).

3 RESULTS

3.1 Patient Characteristics

Sixty four (58.7%) patients were female. Age at recruitment ranged from 18-72 years (mean = 42.0; SD = 14.6), with 10 (9.2%) patients aged 65 or older. Mean age of epilepsy onset was 21.5 years (SD = 17.0). Ten (9.2%) patients had family history of epilepsy. Sixty eight (62.4%) patients had detectable MRI abnormalities. In terms of comorbidity, 19 (17.4%) had neurological deficits, 15 (13.8%) had learning disabilities, and 52 (47.7%) had histories of psychiatric comorbidities. See *Table 1* for breakdown of these statistics by cohort.

TABLE 1. Age, sex and medical background of patients

		True Prospective cohort N = 59	Retrospective-Prospective cohort N = 35	True Retrospective cohort N = 15	Total N = 109
Sex – n (%)					
Male		23 (39.0)	17 (51.4)	5 (33.3)	45 (41.3)
Female		36 (61.0)	18 (48.6)	10 (66.7)	64 (58.7)
Age					
Age at recruitment	Min. – max.	18-72	19-71	19-66	18-72
	Mean (SD)	43.4 (13.8)	41.3 (14.6)	36.5 (17.1)	42.0 (14.6)
	Median (Q1, Q3)	42.0 (33.0, 54.5)	38.0 (30.5, 50.5)	32.0 (22.5, 47.0)	39.0 (30.0, 52.0)
Age at 1st seizure	Min. – max.	0-59	0-67	0-50 ***(N=14)***	0-67 ***(N=108)***
	Mean (SD)	23.4 (16.1)	21.0 (19.0)	14.1 (14.0) ***(N=14)***	21.5 (17.0) ***(N=108)***
	Median (Q1, Q3)	19.0 (13.0, 35.0)	18.0 (7.0, 33.5)	10.0 (4.0, 20.3) ***(N=14)***	18.0 (7.0, 32.3) ***(N=108)***
Duration of epilepsy (years)	Min. – max.	1-69	2-53	3-56 ***(N=14)***	1-69 ***(N=108)***
	Mean (SD)	20.0 (14.1)	20.0 (14.6)	23.6 (14.4) ***(N=14)***	20.3 (14.2) ***(N=108)***
	Median (Q1, Q3)	19.0 (8.0, 28.8)	17.0 (7.0, 33.0)	21.0 (14.3, 31.8) ***(N=14)***	19.0 (8.0, 29.0) ***(N=108)***
Background – n (%)					
Family history of epilepsy		7 (11.9)	3 (8.6)	0 (0.0)	10 (9.2)
MRI abnormality		36 (61.0)	23 (65.7)	9 (60.0)	68 (62.4)
Neurological deficit		9 (15.3)	6 (17.1)	4 (26.7)	19 (17.4)
Learning disability		4 (6.8)	6 (17.1)	5 (33.3)	15 (13.8)
Psychiatric Comorbidity		25 (42.4)	16 (45.7)	11 (73.3)	52 (47.7)

Note: Where data were unavailable, N number used is italicised in bold.

Ninety seven (89.0%) patients had focal epilepsy, 8 (7.3%) had generalised epilepsy (two of them with juvenile myoclonic epilepsy (JME)), and 4 (3.7%) had combined focal and generalised epilepsy. For seizure focus, 56 (51.4%) patients had temporal lobe epilepsy, 14 (12.8%) frontal lobe epilepsy, and 35.8% had other foci. Regarding seizure types, 49 (45.0%) had histories of focal aware seizures; 79 (72.5%) had focal unaware seizures; 73 (67.0%) had focal to bilateral convulsive (tonic-clonic) seizures; 11 (10.1%) had generalised non-motor seizures; 4 (3.7%) had myoclonic jerks; and 10 (9.2%) had generalised tonic-clonic seizures. In total, 83 (76.2%) patients had histories of tonic-clonic seizures of either onset. See *Table 2* for further information.

TABLE 2. Epilepsy type, seizure history, and epilepsy aetiology

n (% cohort)		True Prospective cohort N = 59	Retrospective-Prospective cohort N = 35	True Retrospective cohort N = 15	Total N = 109
Focal epilepsy		52 (88.1)	32 (91.4)	13 (86.7)	97 (89.0)
Seizure history	Focal aware	26 (44.1)	18 (51.4)	4 (26.7)	48 (44.0)
	Focal impaired awareness	44 (74.6)	20 (57.1)	11 (73.3)	75 (68.8)
	Focal to bilateral convulsive	38 (64.4)	24 (68.6)	9 (60.0)	71 (65.1)
Generalised epilepsy		6 (2 JME) (10.2)	1 (2.9)	1 (6.7)	8 (2 JME) (7.3)
Seizure history	Generalised non-motor	6 (10.2)	0 (0.0)	1 (6.7)	7 (6.4)
	Generalised myoclonic jerks	3 (5.1)	1 (2.9)	0 (0.0)	4 (3.7)

	Generalised tonic-clonic	6 (10.2)	1 (2.9)	1 (6.7)	8 (7.3)
Combined focal & generalised onset		1 (1.7)	2 (5.7)	1 (6.7)	4 (3.7)
Seizure history	Focal aware	0 (0.0)	0 (0.0)	1 (6.7)	1 (0.9)
	Focal impaired awareness	1 (1.7)	2 (5.7)	1 (6.7)	4 (3.7)
	Focal to bilateral convulsive	1 (1.7)	1 (2.9)	0 (0.0)	2 (1.8)
	Generalised non-motor	1 (1.7)	2 (5.7)	1 (6.7)	4 (3.7)
	Generalised myoclonic jerks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Generalised tonic-clonic	1 (1.7)	0 (0.0)	1 (6.7)	2 (1.8)
All epilepsies		59 (100.0)	35 (100.0)	15 (100.0)	109 (100.0)
Seizure history	Focal aware	26 (44.1)	18 (51.4)	5 (33.4)	49 (45.0)
	Focal impaired awareness	45 (76.3)	22 (62.9)	12 (80.0)	79 (72.5)
	Focal to bilateral convulsive	39 (66.1)	25 (71.4)	9 (60.0)	73 (67.0)
	Generalised non-motor	7 (11.9)	2 (5.7)	2 (13.3)	11 (10.1)
	Generalised myoclonic jerks	3 (5.1)	1 (2.9)	0 (0.0)	4 (3.7)
	Generalised tonic-clonic	7 (11.9)	1 (2.9)	2 (13.3)	10 (9.2)
Epilepsy aetiology					
Structural		18 (30.5)	8 (22.9)	4 (26.7)	30 (27.5)
Genetic		3 (5.1)	1 (2.9)	0 (0.0)	4 (3.7)
Infectious		2 (3.4)	2 (5.7)	1 (6.7)	5 (4.6)
Metabolic		0 (0.0)	0 (0.0)	1 (6.7)	1 (0.9)
Autoimmune		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown		36 (61.0)	24 (68.6)	9 (60.0)	69 (63.3)

The modal number of previously prescribed ASMs was 4, and median 5 (range = 1 to 15). The majority of patients, 95/109 (87.16%), fulfilled the ILAE definition for 'drug-resistant epilepsy' (DRE), based on a treatment history of ≥3 ASMs [64]. At baseline, 11 (10.1%), 49 (45.0%), 36 (33.0%), 11 (10.1%) and 2 (1.8%) patients were taking 1, 2, 3, 4 and 5 ASMs - including BRV - respectively. Mode and median number of ASMs at baseline was 2 (range = 1 to 5). The most commonly co-prescribed ASM at baseline was Lamotrigine. See *Table 3 for* cohort breakdowns.

TABLE 3. AED History and Duration of BRV Treatment at Study Baseline

		True Prospective cohort N = 59	**Retrospective-Prospective cohort N = 35**	**True Retrospective cohort N = 15**	**Total N = 109**
ASMs					
Number previous ASMs	Min. – max.	1-12	1-12	1-15	1-15
	Mean (SD)	5.6 (2.8)	5.5 (2.8)	6.1 (3.8)	5.6 (2.9)
	Median (Q1, Q3)	5.0 (4.0, 7.5)	5.0 (4.0, 7.0)	5.0 (3.0, 8.5)	5.0 (4.0, 7.0)
Total number ASMs at baseline	Min. – max.	1-5	1-5	1-3	1-5
	Mean (SD)	2.6 (0.8)	2.5 (1.0)	2.1 (0.6)	2.5 (0.9)
	Median (Q1, Q3)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 2.5)	2.0 (2.0, 3.0)
Days retention when recruited to study	Min. – max.	1-219	30-1184	12-457 ***(N=14)***	1-1184 ***(N=108)***
	Mean (SD)	54.0 (60.6)	660.0 (315.2)	164.0 (135.3) ***(N=14)***	264.0 (335.7) ***(N=108)***
	Median (Q1, Q3)	24.0 (14.0, 83.0)	637.0 (444.5, 500.5)	140.0 (55.5, 209.5) ***(N=14)***	99.0 (19.8, 443.3) ***(N=108)***

Note: Where data were unavailable, N number used is italicised in bold. Among the RP cohort, days retention at recruitment ranged from 30 to 1184. Note that three data points in this range fell below the criteria of >7 months BRV retention, reflecting 3 patients who were identified more than 7 months after beginning BRV treatment, but who had withdrawn BRV at the point of first meeting.

3.2 ASM Treatment

Total daily BRV dosage at start of treatment ranged from 25 to 200mg/day (n=109; mean=73.8mg; SD=55.0mg; median=50.0mg; Q1=25.0mg; Q3=100.0mg), with lower dosages for those commencing treatment *de novo* and higher dosages for those switching directly from other ASMs to a BRV equivalent. Maximum dosages reached during treatment ranged from 25 to 300mg/day (mean=146.4mg; SD=59.5mg; median=150.0mg; Q1=100.0mg; Q3=200.0mg) (n=109). This exceeded the licensed range of 50 mg to 200 mg/day in 4 cases. Maintenance dosage was tailored to individuals' responses - with dose reductions required in 20 cases - and at last follow-up ranged from 25 to 300mg/day, exceeding the licensed range in 2 cases (mean=146.1mg; SD=55.1mg; median=150.0mg; Q1=100.0mg; Q3=200.0mg) (n=94: 14 withdrew before 3m follow-up, 1 unavailable). By last follow-up, 17 patients were on BRV monotherapy (of these, 2 had discontinued all other ASMs before commencing BRV, 11 switched from other ASMs to BRV (9 LEV, 1 lacosamide, 1 carbamazepine), and 4 withdrew concomitant ASMs later in the course of BRV treatment (2 lamotrigine, 2 eslicarbazepine). Nine of these 17 patients subsequently withdrew BRV (2 due to lack of efficacy, 6 due to side effects, and 1 for both reasons).

3.3 Retention Rates

Among the TP cohort, 53 (89.8%), 47 (79.7%), 36 (61.0%), 17 (28.8%), and 2 (3.4%) patients completed 3, 6, 12, 18 and 24-month follow-ups, respectively. Among the RP patients (whose initial meetings took place at varying stages of BRV treatment), 29 (82.9%) completed 6-month prospective follow-up, 26 (74.3%) completed 12-month follow-up, and no patients reached 18-month follow up-before study close. For the whole group (n=109), BRV retention rates at key treatment time points were 87.2%, 78.0%, 65.1% and 45.0% at 3, 6, 12 and 18 months, respectively. See *Table 4* for breakdown. At study end, 64.2% (70/109) were still active, 5 (4.6%) had withdrawn consent but remained on BRV, and 34 (31.2%) had stopped BRV. The drug retention rate was 68.8% (75/109). Among those who withdrew BRV treatment, 23/34 (67.6%) patients withdrew due to side effects only, 3 (8.8%) withdrew due to lack of efficacy only, 7 (20.6%) withdrew for both reasons, and 1 (2.9%) patient died from medical complications unrelated to BRV. See *Table 5* for breakdown.

Table 4. Number of patients surpassing each of the study's treatment time points.

n (%)	True Prospective cohort N = 59	Retrospective-Prospective cohort N = 35	True Retrospective cohort N = 15	Total N = 109
Baseline	59 (100.0)	35 (100.0)	15 (100.0)	109 (100.0)
3m	53 (89.8)	32 (91.4)	10 (66.7)	95 (87.2)
6m	47 (79.7)	32 (91.4)	6 (40.0)	85 (78.0)
12m	37 (62.7)	32 (91.4)	2 (13.3)	71 (65.1)
18m	17 (28.8)	32 (91.4)	0 (0.0)	49 (45.0)
24m	2 (3.4)	31 (88.6)	0 (0.0)	33 (30.3)
30m	0 (0.0)	22 (62.9)	0 (0.0)	22 (20.2)
36m	0 (0.0)	13 (37.1)	0 (0.0)	13 (11.9)
42m	0 (0.0)	7 (20.0)	0 (0.0)	7 (6.4)
48m	0 (0.0)	3 (8.6)	0 (0.0)	3 (2.8)

Note: Excluded from rates are those who withdrew BRV treatment, those who withdrew study consent, and those for whom duration of BRV treatment had not yet reached the time-points specified. Among those who withdrew BRV, the specific date of the month of withdrawal was unavailable in 10 cases – here, the median value from the range of possible days' retention was used.

TABLE 5. Study withdrawal and reasons for withdrawal by cohort.

n (%)	True Prospective cohort N = 59	Retrospective-Prospective cohort N = 35	True Retrospective cohort N = 15	Total N = 109

Completed study	42 (71.2)	28 (80.0)	0 (0.0)	70 (64.2)
Withdrew from BRV treatment	14 (23.7)	5 (14.3)	15 (100.0)	34 (31.2)
Withdrew consent	3 (5.1)	2 (5.7)	0 (0.0)	5 (4.6)
Total withdrawn	17 (28.8)	7 (20.0)	15 (100.0)	39 (35.8)
Reason for BRV withdrawal	N = 14	N = 5	N = 15	N = 34
Side effects only	8 (57.1)	4 (80.0)	11 (73.3)	23 (67.6)
Lack of efficacy only	2 (14.3)	0 (0.0)	1 (6.7)	3 (8.8)
Side effects & lack of efficacy	3 (21.4)	1 (20.0)	3 (20.0)	7 (20.6)
Death	1 (7.1)	0 (0.0)	0 (0.0)	1 (6.7)

The duration of treatment recorded at either last follow-up or BRV withdrawal date ranged from 6 to 1514 days (median = 384.0; Q1 = 183.0; Q3 = 804.3; n=108, data unavailable for 1 patient). Among those who withdrew treatment this was 6 to 1027 days (median = 113.0; Q1 = 49.0; Q3 = 205.0; n = 33, data unavailable for 1 patient), and among those who remained on BRV for the entirety of the study this was 182 to 1514 days (median = 558.5 days; Q1= 376.3; Q3 = 906.0; n = 70). Figure 2 shows the Kaplan-Meier survival curves for each cohort, and for all cohorts combined, representing the probability of remaining on BRV (y-axis) beyond a given number of days BRV retention (x-axis). Retention modelling using these curves predicted that among the TP cohort, 82.0% of patients would still be undergoing BRV treatment at 6 months, and 78.0% at 12 months. Among the RP cohort, 91.0% of patients would still be undergoing BRV treatment at 6 months, and 91.0% at 12 months, and among the TR cohort, 14.0% of patients would still be undergoing BRV treatment at 6 months, and 0.0% at 12 months. With all 3 cohorts combined, retention modelling predicted that 74.0% and 70.0% patients would still be taking BRV at 6 months and 12 months, respectively. Available data for >12 months were considered unreliable due to high levels of censoring.

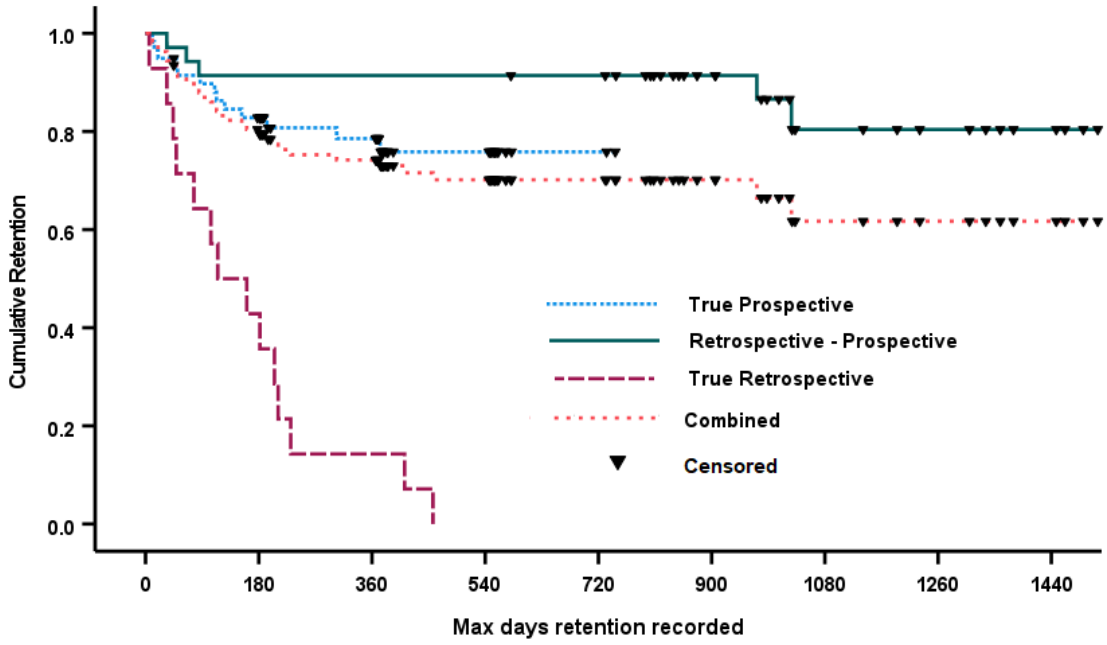

FIGURE 2. Kaplan Meier function. Date of withdrawal was unavailable for 1 patient in the TR cohort, and as such in the above function n=14 for this cohort and n=108 for whole group. Drops in cumulative survival mark the time points at which patients withdrew BRV treatment. Censored points indicate the last points of contact with patients who were, at the time, still being treated with BRV (including the 5 patients who withdrew study consent).

3.4 Efficacy Outcomes

3.4.1 Responder Rates

For the TR cohort, examination of clinic notes indicated global impressions of ineffective seizure control in 9/15 (60.0%) patients, seizure reduction in 3/15 (20.0%) patients, and seizure freedom in 1/15 (6.7%) patient. Seizure-related information was unavailable in 2/15 (13.3%). Combined TP and RP cohort data (n = 94) showed

that 28 of the 91 patients with quantifiable seizure frequency available at final study follow-up experienced ≥50% seizure reduction from baseline, yielding an overall ≥50% responder rate of 30.8%. More specifically, 8 (8.8%) had withdrawn BRV before reaching first study time-point, 45 (49.5%) were non-responders (<25% reduction), 10 (11.0%) were marginal responders (≥25 - <50% reduction), 17 (18.7%) had ≥50 - <100% reduction, and 11 (12.1%) obtained seizure freedom. Combined TP and RP data showed that at last follow up, there was no statistically significant difference between the ≥50% responders (n=28) and those with <50% seizure reduction (n=55) for number of previous ASMs (mean=4.7 and range=1 to 8, vs. mean=5.9 and range=1 to 12 respectively, p=.13), or for BRV maintenance dosage (mean=139.6mg/day and range=35.0 to 200.0mg/day, vs mean=156.9mg/day and range=25.0 to 300.0mg respectively, p=.13). However, for the third measure of epilepsy intractability - number of current ASMs - ≥50% responders had significantly lower means than those with <50% seizure reduction (mean=1.9 and range=1 to 3, vs. mean=2.4 and range=1 to 5, p=.013).

Figure 3 shows responder rates among the TP cohort at discrete study time points compared to baseline. ≥50% responder rates (50-100% reduction) were 21/57 (36.8%), 17/51 (33.3%), 11/37 (29.7%), 3/17 (17.6%) and 1/2 (50.0%) at 3, 6, 12, 18 and 24 months, respectively. Among these patients, 5/57 (8.8%), 4/51 (7.8%), 4/37 (10.8%), 1/17 (5.9%) and 0/2 (0.0%) were seizure-free at 3, 6, 12, 18 and 24 months, respectively. Overall, 7 patients in this cohort were seizure-free for the duration of at least one 3-month study follow-up interval (3/7 were already seizure-free at baseline and maintained this). Four (11.4%) patients were seizure-free for the duration of at least one 6-month study follow-up interval (3/4 were seizure-free at baseline), and seizure freedom was maintained for all 4 until study cessation. Inspection of *Figure 3* suggests that responder rates were similar at the separate time points and at last available follow-up, despite the latter varying across patients.

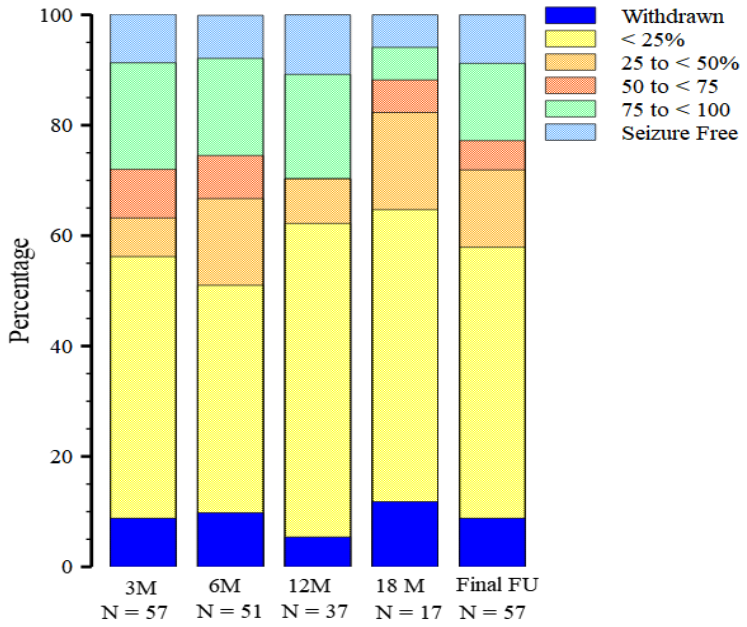

FIGURE 3. TP cohort responder rates at 3, 6, 12, 18-month and final follow-ups, compared to baseline. *X*-axis shows study follow-up, and *y*-axis shows percentage of patients in each of the responder rate categories. Legend provides colour key for responder rate categories. 24-month follow-up was omitted due to insufficient data (n=2, 14 had withdrawn BRV, 3 had withdrawn consent and 40 had not reached 24 months retention). ≥50% responder rate is sub-categorised into those achieving 50 - <75% seizure reduction, 75 - <100% seizure reduction, and seizure freedom. 25 - <50% reduction represents marginal improvement. <25% reduction represents non-responders, including those with seizure increase. 'Final FU' represents patients' last available follow-up periods. N-numbers provided exclude those who had withdrawn BRV during previous follow-up periods or withdrawn study consent, those for whom data were unavailable, and those who had not yet reached the follow-up in question. At 3m, 1 had withdrawn consent and 1 had unavailable data. At 6m, 5 had withdrawn BRV, 2 had withdrawn consent and 1 had unavailable data. At 12m, 10 had withdrawn BRV, 3 had withdrawn consent, 1 had unavailable data and 8 were incomplete. At 18m, 12 had withdrawn BRV, 3 had withdrawn consent, 2 had unavailable data and 25 were incomplete. At last available follow-up, 1 had withdrawn before completing any follow-ups, and 1 had unavailable data.

3.4.2 Seizure Freedom

Seizure freedom rates could be reliably calculated both retrospectively and prospectively and therefore they included the full study cohort. In total, 18/109 (16.5%) patients were seizure free for at least 3 consecutive months of treatment, 15 (13.8%) for at least 6 months and 7 (6.4%) for at least 12 months. Twelve of 109 (11.0%) maintained seizure freedom until the end of follow-up (4 patients from the TP, 7 from RP and 1 from TR cohort). Of these, one had unknown baseline status, 3 maintained their baseline seizure freedom, and 8 became seizure free *de novo*. Data from all 3 cohorts combined showed that last follow up, there was no statistically significant difference between those with (n=12) and those without seizure freedom (n=77) for number of previous ASMs (mean=4.5 and range=1 to 8, vs. mean=5.7 and range=1 to 12 respectively, p=.24), number of current ASMs (mean=1.8 and range=1 to 3 ,vs. mean=2.3 and range=1 to 5 respectively, p=.072), or BRV dosage (mean=123.3mg/day and range=35.0 to 200.0mg/day vs mean=149.5mg/day and range=25.0 to 300.0mg/day respectively, p=.13). Note that in all 3 of these measures of epilepsy intractability, means were numerically lower in those who were seizure-free at last follow-up vs those who were not.

3.4.3 Monthly Seizure Frequency

Overall among the TP cohort, the Wilcoxon signed-rank test detected little change in monthly average seizure frequency at various study intervals and for different seizure types (see *Supplementary Material* for full results). See *Figure 4* for corresponding graphs. Analyses revealed a significant reduction in focal aware monthly seizure frequency at 3 months (n = 46, mean = 9.6, SD = 41.8, median = 0.0, IQR = 3.1) compared to at baseline (n=52, mean = 26.4, SD = 118.6, median = 0.0, IQR = 4.8), z = -2.5, p = .013, with a small effect size, r = .26. For tonic-clonic seizures (focal-to-bilateral convulsive and generalised combined), a significant reduction was detected at 12 months (n = 36, mean = .55, SD = 2.1, median = 0.0, IQR = .13) compared to at baseline (n=59, mean = .85, SD = 2.5, median = 0.0, IQR = .33), z = -2.0, p = .042, with a small effect size, r = .24. For all seizure types combined, analyses revealed a significant reduction in seizure frequency at 3 months (n = 53, mean = 17.4, SD = 47.2, median = 3.0, IQR = 12.8) compared to at baseline (n=59, mean = 51.4, SD = 152.1, median = 5.0, IQR = 18.7), z = -2.2, p = .031, with a small effect size, r = .21. Both TP and RP cohort data were combined for analyses at last available follow-up. When all seizures of all types recorded throughout follow-up were included, average monthly seizure frequency had decreased by 13.3%, from 5.0 at baseline to 4.3 at last follow-up, however this reduction did not reach statistical significance, p = .35. When only seizures recorded throughout the last available follow-up period (e.g. 6 to 12 months) were considered, there was a significant reduction in tonic- clonic seizures from baseline (n=93, mean = .91, SD = 2.4, median = 0.0, IQR = .67) to last follow-up (n = 85, mean = .54, SD = 1.6, median = 0.0, IQR = .33), z = -2.0, p = .045, with a small effect size, r = .15. Tonic-clonic seizure frequency was explored further among those reporting tonic- clonic seizures either at baseline or last follow-up (n=36): 21/36 (58.3%) patients showed a decrease in tonic-clonic seizures/month from baseline to last available follow-up, 2/36 (5.6%) showed no change, and 13/36 (36.1%) showed increased seizure frequency. Nine of 36 (25.0%) had achieved complete tonic-clonic seizure freedom by last follow-up.

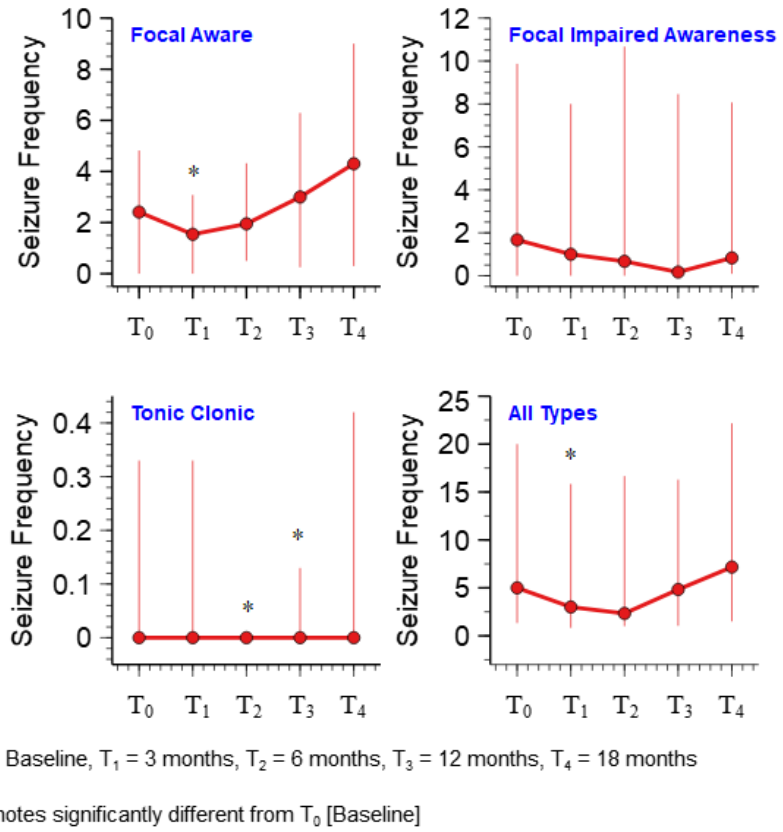

FIGURE 4. For the True Prospective cohort, the medians of mean average monthly seizure frequency are plotted at each follow-up for 1) focal aware seizures (top left), 2) focal impaired awareness seizures (top right), 3) tonic clonic seizures (focal-to-bilateral convulsive and generalised combined) (bottom left), and 4) all seizure types combined (bottom right). 24-month follow-up was omitted from analyses due to insufficient data. N-number available varied across seizure types and follow-ups. The lower ends of the vertical red bars indicate Q1, and the higher ends, Q3. The Wilcoxon signed-rank test compared monthly seizure frequency at baseline to at each follow-up, allowing for significant changes to be detected even when median remained unchanged. Asterisks (*) denote significant changes in seizure frequency from baseline, all of which were decreases.

3.4.4 Seizure Frequency Category changes

For the TP and RP cohorts combined, category improvements (i.e. reductions) in seizure frequency from baseline to last follow-up were seen in 31.4% (27/86) patients with available data. 44.2% (38/86) patients remained in the same category, whilst deteriorations were observed in 24.4% (21/86) patients.

3.5 Tolerability & Safety Outcomes

3.5.1 Treatment-emergent Adverse Events

Throughout the study, 100/109 (91.7%) patients reported at least one treatment-emergent adverse event (TEAE) when asked about possible side effects of BRV. Numbers of TEAEs reported by each patient ranged from 0 to 21, with a median of 4 (Q1 = 2, Q3 = 6). A TEAE was considered persistent if upon emergence it was reported consistently until the end of follow-up, intermittent if it's reporting was inconsistent, and transient if it resolved after a limited period. The proportions of persistent, intermittent and transient TEAEs reported were 58.4%, 5.3% and 36.2%, respectively. In total, 78/109 (71.6%) patients reported at least 1 *persistent* side effect. TEAEs had most commonly (median and mode) emerged in the first 3 months of treatment with 321/505 (63.6%) individual TEAEs reported in this period. Transient side effects had most commonly (median and mode) resolved by 6 month follow up, by which time, 110/183 (60.1%) transient TEAEs were no longer present.

The rates of reporting at least one TEAE for the TP, RP and TR cohorts were 91.5%, 88.6%, and 100.0% respectively, p=.49, lending support to the inclusion of both prospective and retrospective data in the ensuing analyses. *Table 6* lists side effects reported in over 10% of patients (see *Appendix B* for complete list).

TABLE 6. Frequently reported adverse events (reported by ≥10% of patients).

Side effect	N (%)	n (%) of N with HX of Psychiatric Comorbidity	N (%) persistent	N (%) intermittent	N (%) transient
Fatigue	**33 (30.3)**	5 (15.2)	21 (19.3)	4 (3.7)	8 (7.3)
Irritability *	**32 (29.4)**	4 (12.5)	18 (16.5)	2 (1.8)	12 (11.0)
Depression/low mood *	**31 (28.4)**	19 (61.3)	23 (21.1)	1 (0.9)	7 (6.4)
Increase in seizure frequency	**31 (28.4)**	13 (41.9)	25 (22.9)	3 (2.8)	3 (2.8)
Sleep disturbance	**27 (24.8)**	11 (40.7)	13 (11.9)	4 (3.7)	10 (9.2)
Anger *	**20 (18.3)**	12 (60.0)	14 (12.8)	1 (0.9)	5 (4.6)
Somnolence / sedation	**20 (18.3)**	12 (60.0)	11 (10.1)	4 (3.7)	5 (4.6)
Headache	**19 (17.4)**	15 (78.9)	11 (10.1)	1 (0.9)	7 (6.4)
Rapidly fluctuating mood *	**18 (16.5)**	10 (55.6)	9 (8.3)	1 (0.9)	8 (7.3)
Nausea	**18 (16.5)**	12 (66.7)	7 (6.4)	0 (0.0)	11 (10.1)
Unsteadiness	**17 (15.6)**	10 (58.8)	10 (9.2)	0 (0.0)	7 (6.4)
Memory problems	**17 (15.6)**	12 (70.6)	13 (11.9)	0 (0.0)	4 (3.7)
Confusion / mental slowing	**17 (15.6)**	12 (70.6)	7 (6.4)	1 (0.9)	9 (8.3)
Dizziness	**17 (15.6)**	10 (58.8)	9 (8.3)	0 (0.0)	8 (7.3)
Aggression *	**13 (11.9)**	9 (69.2)	8 (7.3)	0 (0.0)	5 (4.6)
Increased anxiety *	**13 (11.9)**	12 (92.3)	9 (8.3)	0 (0.0)	4 (3.7)
Gastro-intestinal disturbance	**13 (11.9)**	5 (38.5)	6 (5.5)	1 (0.9)	6 (5.5)
Suicidal ideation *	**11 (10.1)**	10 (90.9)	6 (5.5)	0 (0.0)	5 (4.6)

Note: Asterisks indicate psychiatric AEs. AEs reported by <10% of patients: pins & needles/numbness (n=10, 9.2%), weight loss (n=9, 8.3%), depersonalisation/abnormal thoughts, limb/joint pain (both n=8, 7.3%), changes to menstrual period, constipation, word finding difficulties (all n=7, 6.4%), slurred speech (n=6, 5.5%), frequent need to pass urine, double vision (both n=4, 3.7%), skin irritation, breathlessness, tremor, dehydration/increased thirst, loss of sex drive, migraines, paranoia, night sweats, concentration difficulties, weight gain, light-headedness, avolition, increased focal aware seizures (all n=3, 2.8%), ringing in ear, increased contusion, visual disturbance, vomiting, reduced 'warning' before seizure, hallucinations, extremities of mood, dry mouth (all n=2, 1.8%), psychosis, tooth grinding/cheek biting, cold hands and feet, increased pain sensitivity, loss of appetite, vivid dreams, more violent seizure clusters, increase in heart rate & blood pressure, increased emotional sensitivity, argumentativeness, hair loss, chest pains, general malaise (all n=1, 0.9%).

The most commonly reported side effects were fatigue, irritability and depression/low mood, reported at least once by 30.3%, 29.4% and 28.4% of patients respectively, and *persistently* by 19.3%, 16.5% and 21.1% of patients respectively. At 3m (N available = 95), 6m (N=84), 12m (N=70), 18m (N=41) and 24m (N=16), fatigue was reported by 13.7%, 13.1%, %, 14.3%, 12.2% and 12.5% of patients, irritability by 21.1%, 11.9%, 7.1%, 7.1%, 14.6% and 12.5% of patients, and depression/low mood by 16.8%, 9.5%, 7.1%, 12.2% and 6.3% of patients, respectively. In total, 63 (57.8%) patients reported PAEs. Dermatological, cardiological and haematological TEAEs were rare (2.8%, 0.9% and 0%, respectively). A >25% increase in seizures at a given follow-up compared to baseline was identified at least once in 31 (28.4%) patients, and *persistently* in 25 (22.9%) patients. Eighty-one AEs *unrelated* to BRV were reported, most commonly epilepsy-related hospital admissions (n=37). Permanent discontinuation of BRV due to TEAEs alone, or due to both TEAEs and lack of efficacy, occurred in 30 patients (27.5% of the whole cohort, or 30.0% of those reporting side effects); the most common TEAEs among this group were depression/low mood (50.0%), irritability (43.3%), fatigue (30.0%) and anger (30.0%).

3.5.2 Psychiatric Adverse Events

Sixty-three (57.8%) patients reported at least one PEA (see *Table 6* and *Appendix B*) throughout follow-up. Over half (54.0%, 34/63) of these patients had histories of psychiatric comorbidities. For the whole cohort, the most frequently reported PAEs were irritability (29.4%; of whom 12.5% had psychiatric histories), depression/low mood (28.4%; of whom 61.3% had psychiatric histories), and anger (18.3%; of whom 60.0% had psychiatric histories). Overall, 11 (10.1%) patients reported suicidal ideation related to, or possibly related to BRV, and there was 1 case of attempted suicide deemed related to the drug. Of these 11 patients, 9 (81.8%) had histories of depression, 1 (9.0%) had a history of a different psychiatric comorbidity, and 1 (9.0%) had no

known psychiatric history. Treatment was withdrawn in 5/11 cases (45.5%; 4.6% of the full study cohort). There was no significant correlation between the reporting of suicidal ideation and DRE (as defined by ILAE [64]), p = .15.

3.5.3 Wellbeing Questionnaires

There were no significant changes in mean BDI scores over time for the TP cohort or the RP cohort, p = .91 and .97, respectively, or in mean BAI anxiety scores for the two cohorts, p = .99 and .95, respectively. QOLIE scores showed no significant changes over time for the RP cohort, p = .85, but a significant increase across study timepoints for the TP cohort, indicating improved quality of life over time, p = .017. Mean scores here were 55.3 (baseline), 59.5 (3m FU), 63.8 (6m FU), 66.7 (12m FU) and 67.7 (18m FU). See *Appendices C, D* and *E* respectively for all mean and median scores of the BDI, BAI and QOLIE questionnaires at each follow-up.

3.6 Subgroup Analyses

Key demographics among the 4 subgroups of interest (those with learning disabilities (n = 15); those with history of psychiatric comorbidities (n = 51); those 65 years of age or older at recruitment (n = 10); and those with previous exposure to LEV (n = 99)) were compared to the rest of the population (see *Table 7*). Of note, those with learning disabilities were significantly younger than those without, both at 1st seizure and at study recruitment, p<.001

TABLE 7. Patient demographics in subgroups of interest, compared to the rest of the cohort.

		LEV-prior	LEV-naive	**Learning Disability**	No Learning Disability	**History of Psychiatric Comorbidity**	No History of Psychiatric Comorbidity	**Over 65s**	Under 65s
		N = 99	N = 10	N = 15	N = 94	**N = 52**	N = 57	**N = 10**	N = 99
Age									
Age at recruitment	Min – max.	**18-72**	21-72	**18-53**	19-72	**21-66**	18-72	**65-72**	18-63
	Mean (SD)	**41.6 (14.2)**	45.4 (18.7)	**29.2 (9.2)**	44.0 (14.3)	**31.6 (13.6)**	42.2 (15.6)	**68.8 (3.0)**	39.2 (12.4)
	Median (Q1, Q3)	**39.0 (30, 51.5)**	52.5 (26.8, 58.8)	**29.0 (21.5, 34.0)**	42.5 (33.3, 54.8)***	**40.0 (28.8, 52)**	39.0 (30.0, 54.0)	**70.0 (66.0, 71.0)*****	38.0 (29.0, 48.5)
Duration of epilepsy (years)	Min – max.	**1-56 *(N=98)***	2-69	**8-53 *(N=14)***	1-69	**1-56**	1-69 ***(N=56)***	**7-69**	1-53 ***(N=98)***
	Mean (SD)	**20.3 (13.5) *(N=98)***	20.3 (22.0)	**25.7 (14.4) *(N=14)***	19.5 (14.4)	**19.5 (15.0)**	20.9 (13.6) ***(N=56)***	**27.5 (21.5)**	19.5 (13.2) ***(N=98)***
	Median (Q1, Q3)	**19.0 (9.0, 29.0) *(N=98)***	18.0 (2.0, 31.0)	**22.0 (19.0, 33.5) *(N=14)***	18.0 (8.0, 29.0)	**13.0 (8.0, 29.0)**	21.0 (9.8, 29.5) ***(N=57)***	**21.0 (11.5, 39.0)**	19.0 (8.0, 29.0) ***(N=98)***
Age at 1st seizure	Min – max.	**0-67 *(N=98)***	0-58	**0-21 *(N=14)***	1-67	**0-65 *(N=51)***	0-67	**3-67**	0-58 ***(N=98)***
	Mean (SD)	**21.4 (16.5) *(N=98)***	22.7 (21.5)	**4.2 (7.6) *(N=14)***	24.1 (16.4)	**22.3 (14.6) *(N=51)***	20.8 (18.8)	**42.4 (22.9)**	19.4 (14.8) ***(N=98)***
	Median (Q1, Q3)	**18.0 (7.0, 32.3) *(N=98)***	19.5 (3.8, 40.8)	**0.0 (0.0, 5.5) *(N=14)***	19.0 (13.0, 36.3)***	**20.0 (13.0, 27.0) *(N=51)***	16.0 (4.5, 35.0)	**50.0 (18.3, 60.5)****	18.0 (7.0, 27.0) ***(N=98)***
Sex - n (%)									
Male		**39 (39.4)**	6 (60.0)	**8 (53.3)**	37 (39.4)	**21 (41.2)**	24 (41.4)	**5 (50.0)**	40 (40.4)
Female		**60 (60.6)**	4 (40.0)	**7 (46.7)**	57 (60.6)	**30 (58.8)**	34 (58.6)	**5 (50.0)**	59 (59.6)
Epilepsy type – n (%)									
Focal onset		**87 (87.9)**	10 (100.0)	**9 (60.0)**	88 (93.6)	**47 (90.4)**	50 (87.7)	**10 (100.0)**	87 (87.9)
Generalised onset		**8 (8.1)**	0 (0.0)	**2 (13.3)**	6 (2 JME) (6.4)	**4 (1 JME) (7.7)**	4 (1 JME) (7.0)	**0 (0.0)**	8 (2 JME) (8.1)
Combined onset		**4 (4.0)**	0 (0.0)	**4 (26.7)**	0 (0.0)	**1 (1.9)**	3 (5.3)	**0 (0.0)**	4 (4.0)

Note: Where data were unavailable, N number is italicised in bold. Values annotated with asterisks ('*') were significantly greater than the corresponding value of the comparator subgroup. * p < .05; ** p < .005; *** p < .001.

3.6.1 Patients with Previous Levetiracetam Exposure

There were no significant differences in average monthly seizure frequencies from baseline to last follow up between those with prior exposure to LEV (n = 43, median decrease per month of 0.17 seizures) and those without (n=6, median increase per month of 2.01 seizures), p = .35, Mann-Whitney U test. The ≥50% responder rates (22.2% without previous LEV exposure, n=9 *vs.* 28.4% with previous LEV exposure, n=95) also did not differ, p = .52, Fisher's exact test.

Of the 99/109 (90.8%) patients with previous exposure to LEV, 64 (64.6%) had withdrawn LEV due only to side effects, 20 (20.2%) due only to insufficient efficacy, 10 (10.1%) due to both and 5 (5.1%) for reasons unknown. Forty of 99 (40.4%) had switched directly to BRV. Twenty-eight of 99 (28.3%) went on to withdraw BRV treatment, with 6/28 (21.4%) switching back to LEV. Among those previously intolerant to LEV (N=74, 5 unknown), the most frequent side effects to emerge on BRV were fatigue, depression/low mood, and irritability, described by 37.8%, 33.8% and 33.8% of the group, respectively. Previous intolerance to LEV did not appear to be a predictor of intolerance to BRV; rates of reporting at least one TEAE on BRV, BRV withdrawal for any reason, or BRV withdrawal due to side effects did not differ between those with (n=74) and those without history of previous LEV intolerance (n=30; including those who withdrew LEV due to lack of efficacy only, and LEV-naive patients), p = .12, 1.00 and 1.00, respectively. The only side effects of BRV that were reported more frequently by patients previously intolerant of LEV were unsteadiness (21.6% of those with history of LEV intolerance vs. 3.3% of those without), p = .021, OR = 8.0 (95% CI: 1.0, 63.3), and fatigue (37.8% of those with history of LEV intolerance vs. 13.3% of those without), p = .018, OR = 4.0 (95% CI: 1.3, 12.5). Previous history of psychiatric comorbidities among the subgroup who had made a direct switch from LEV to BRV treatment (19/40; 47.5%) did not appear to predict the development of at least one PAE on BRV, p>.05. Increased anxiety was the only specific TEAE with a higher incidence among those with a history of psychiatric comorbidity compared to those without (21.1% *vs* 0.0%), p = .042.

Throughout follow-up, 25 patients who had previously trialled LEV offered spontaneous and direct comparisons regarding the tolerability of LEV vs BRV. They were asked to position their experiences of BRV tolerability on a 5-point scale from significantly worse to significantly better than LEV tolerability. With the caveat of small sample size and low power, 16 (64.0%) patients described BRV tolerability as 'significantly better'. Among the 22 (88.0%) patients who reported feeling marginally or significantly better on BRV, improvements in mood, behaviour, and/or energy levels were cited in 20/22 (90.9%) of cases.

3.6.2 Patients with History of Psychiatric Comorbidity

Among the patients with histories of psychiatric comorbidities (N=52), the most frequently experienced side effects were irritability (38.5%) , depression/low mood (36.5%), and fatigue (36.5%). There was no significant difference between the proportions of patients with and without histories of psychiatric comorbidity reporting at least one TEAE of any kind across the course of the study (96.2% vs 87.7%, respectively), p = .17. Of the non-psychiatric side effects, only headache was reported significantly more frequently in those with psychiatric histories (28.0%) compared to those without (7.0%), p = .004, OR = 5.4 [95% CI: 1.7, 17.5]. Regarding psychiatric side effects, there was no significant difference between the proportions of patients with (65.4%) and without (50.9%) histories of psychiatric comorbidity reporting at least one PAE during the study period, p=.17. Of the specific PAEs, suicidal ideation was reported significantly more frequently in those with psychiatric histories (19.2%) compared to those without (1.8%), p = .003, OR = 13.3 [95% CI: 1.6, 108.3]. Increased anxiety was also reported at a significantly higher rate in those with (23.1%) compared to those without (1.8%) psychiatric histories, p = .001, OR = 16.8 [95% CI: 2.1, 134.5]. There were no significant relationships between psychiatric history status and the reporting of any of the other psychiatric side effects (p > .05).

We explored the relationship between psychiatric history and the reporting of depression/low mood on BRV in more detail by re-running analyses using 3 sub-categories of psychiatric history: depression (n=41), other psychiatric comorbidities (n=11), and no known psychiatric history (n=57). Of the 31 patients who reported

depression/low mood on BRV treatment, 17 (54.8%) had pre-existing history of depression, 2 (6.5%) had history of other psychiatric comorbidities, and 12 (38.7%) had no psychiatric history. There were no significant differences between the rates of reporting depression/low mood in these 3 groups (41.5% (17/41), 18.2% (2/11), and 21.1% (12/57), respectively), p=.078. As such, history of depression did not appear to predict increased reporting of depression/ low mood on BRV.

Among the patients who reported suicidal ideation on BRV, the majority had histories of depression (9/11, 81.8%), 1 had a history of another psychiatric comorbidity and 1 had no known psychiatric history. A significant difference was detected between the rates of reporting suicidal ideation on BRV in those with a history of depression (9/41; 22.0%), history of other psychiatric comorbidities (1/11; 9.1%), and no psychiatric histories (1/57, 1.8%), p = .004. Post hoc analyses revealed a significant difference between the suicidal ideation rates of the 'history of depression' and 'no psychiatric history' groups, p = .002, OR = 15.9 [95% CI: 1.9, 125.0]), but there was no difference between the 'history of depression' vs. 'history of other psychiatric comorbidities' groups (p=.67), or between the 'history of other psychiatric comorbidities' vs 'no psychiatric history' groups (p=.30). Overall, rates of suicidal ideation were significantly higher in those with history of depression compared to those without (i.e. those in the 'other psychiatric comorbidities' and the 'no psychiatric histories' groups combined), p = .002, OR = .11 [95% CI: .022, .53], suggesting that history of depression was a predictor of suicidal ideation on BRV.

Similar analyses considered the relationship between specific history of and reporting of anxiety. Across the cohort, 26 had histories of anxiety, 26 had histories of other psychiatric comorbidities, and 57 had no psychiatric history. Among the 13 patients reporting increased anxiety, 5 (38.5%) had pre-existing history of anxiety, 7 (53.8%) had history of other psychiatric comorbidities, and 1 (7.7%) had no psychiatric history. There were significant differences between the rates of reporting increased anxiety at least once on BRV in those with a history of anxiety (5/26; 19.2%), history of other psychiatric comorbidities (7/26; 26.9%), and no psychiatric histories (1/57, 1.8%), p = .001. Post hoc analyses showed that both those with a history of anxiety and of other psychiatric comorbidities were significantly more likely to report increased anxiety on BRV than those without psychiatric histories, p = .011 and .001 respectively, OR = 13.3 [95% CI: 1.5, 125.0] and 20.8 [95% CI: 2.4, 166.7], respectively. Those with a history of anxiety were no more likely to report anxiety than those with a history of other psychiatric comorbidities, or than those without history of anxiety (i.e. those in the 'other psychiatric comorbidities' and the 'no psychiatric histories' groups) p = .74 and .30, respectively, suggesting that specific history of anxiety did not predict increased anxiety with BRV.

Analyses also explored whether specific histories of psychosis predicted the reporting of psychosis, hallucinations, depersonalisation/abnormal thoughts, or paranoia on BRV. No significant effects were found, p = .49, 1.0, .20 and .25, respectively. Insufficient data were available concerning histories of behavioural disturbance to explore whether this predicted the emergence of behavioural disturbances on BRV.

3.6.3 Patients with Learning Disability

In those with LD, the most commonly reported side effects were anger and fatigue, reported at least once by 40.0% and 33.3% of patients, respectively. Irritability, aggression and increases in seizure frequency followed, each reported by 26.7% patients in this subgroup. There was no significant difference between the rates of reporting at least one TEAE among those with LD (100.0%) compared to those without LD (90.4%), p = .36. Anger was reported significantly more frequently in those with LD (40.0%) vs those without (14.9%), p = .031, OR = 3.8 [95% CI: 1.2, 12.4). No other significant associations were found between LD status and other TEAEs (all p > .05), including, of particular interest, fatigue (p = .77) and somnolence/sedation (p = 1.0).

3.6.4 Patients of Older Age

Among over-65s (N=10), fatigue was the most common side effect, reported in 30.0% of patients. Somnolence/sedation, unsteadiness, headache and light-headedness were all reported at rates of 20.0%. Over-65s reported at least one TEAE throughout the study at a rate of 90.0%, and under-65s at a rate of 91.9%. The difference was not significant, p = .59. Rates of specific TEAEs differed significantly only in the case of light-headedness, which was reported by 20.0% of over-65s vs 1.0% of under-65s, p = .022, OR = 24.5 (95% CI: 2.0, 300.4). One from the over-65 subgroup died, unrelated to BRV. Two of 10 (20.0%) withdrew BRV, both due entirely to side effects.

4 DISCUSSION

BRIVEST was a "real life" observational study following 109 consecutive, unselected adult patients with epilepsy receiving BRV treatment in our centre (58.7% female, mean age = 42 years, range: 18 to 72). The study cohort was heterogeneous, with adequate representation of those with histories of psychiatric comorbidities (n=52), with learning disabilities (n=15) and of older age (n=10). Reflecting the "off-label" prescribing of BRV common in epilepsy clinics [58,65], BRV was administered to 8 patients with generalised idiopathic epilepsy (2 with JME), to 4 patients with combined focal and generalised epilepsy, to 17 patients as monotherapy, and to 4 patients at doses exceeding 200mg daily at some point during their follow up. These factors, together with a follow-up period ranging from 3 to 24 months, allowed for suitable exploration of the 'real-world' efficacy and tolerability of BRV. To avoid selection bias towards those responding well to treatment, we included 3 cohorts: the 'true prospective' (TP) cohort comprised those who commenced BRV treatment less than 6 months before, or any time after, study start (with predominantly prospective data collection); the 'retrospective-prospective' (RP) cohort comprised those who commenced treatment more than 6 months before study start (with a mix of retrospective and prospective data collection); and the 'true retrospective' (TR) cohort comprised those who had discontinued BRV treatment prior to study start (with exclusively retrospective data collection). Overall, via a range of efficacy, tolerability and safety measures, BRV was found to be an effective drug in what was a largely drug-resistant population with high seizure burden (87.2% met the ILAE criteria for DRE [64]).

4.1 Retention

Overall study retention was 64.2%, with 70/109 patients active at study endpoint. Five (4.6%) patients remained on BRV but withdrew study consent. Thirty-four patients (31.2%) withdrew BRV; 23 due to side effects only (21.1% of whole cohort, 67.6% of those who withdrew BRV), 3 due to lack of efficacy only (2.8% of whole cohort, 8.8% of those who withdrew BRV), 7 for both reasons (6.4% of whole cohort, 20.6% of those who withdrew BRV), and 1 due to death unrelated to BRV (0.9% of whole cohort, 2.9% of those who withdrew BRV). This gave an overall drug retention rate of 68.8% at study endpoint. BRV withdrawal rates for all reasons (31.2%), and solely or partly due to side effects (27.5%) were comparable to retention rates reported in two similarly-sized prospective 'real-world' studies of BRV; withdrawal rates overall and specifically due to side effects were 37% and 21%, respectively in one (n=134, [43]), and 34.3% and 30.6%, respectively in the other (n=108, [44]). Our BRV retention rates at separate study time points were 87.2%, 78.0%, 65.1% and 45.0% at 3, 6, 12 and 18 months, respectively. Retention modelling using Kaplan-Meier survival curves predicted that 74.0% of all patients would remain on BRV treatment after 6 months, and 70.0% after 12 months, in line with the 12-month predicted retention rates of similar studies, for example 68.7% [38], 70.4% [36]; and 61.1% [41]. Median duration of treatment was 113 days at date of withdrawal for those who withdrew BRV, compared with 384 days at last available follow-up/date of withdrawal for the whole cohort.

4.2 Efficacy

For the TP and RP cohorts combined, there was a 30.8% (28/91) ≥50% responder rate (≥50% seizure reduction) at last available follow-up compared to baseline, with 12.1% of these patients achieving seizure freedom. An additional 11.0% patients were marginal responders (≥25 - <50% seizure reduction), whilst 49.5% were non-responders (<25% reduction). The remaining 8.8% had withdrawn BRV before reaching the first (3-month) study follow-up. Given the variable durations of BRV treatment at 'last available follow-up', we also assessed responder rates at individual study time points for the TP cohort (i.e. 3, 6, 12 and 18 months retention – insufficient data at 24 months) and, encouragingly, responder rates at last follow-up fell within these ranges (see *Figure 3*). Our ≥50% responder rate at last follow-up (30.8%) was in line with the 28% and 29% reported at last follow-up by 2 similar prospective real-world studies, although their seizure freedom rates were slightly lower, both at 7% [see [42] and [43] respectively]. The 3rd known prospective real-world study of BRV reported higher equivalent ≥50% responder and seizure freedom rates of 40.0% and 21.3% [44], which was not surprising given their shorter 6-month follow-up and consequently limited ability to capture later seizure recurrence. As expected, results of the identified *retrospective* 'real-world' studies of BRV treatment varied more widely than those of prospective studies, with ≥50% responder rates ranging from 21% to 71%, and seizure freedom rates from 7% to 36% [28,36–41]. Again, higher-end efficacy rates [28] could be, in part,

attributable to shorter follow-up, whilst lower-end rates [38] were possibly related to the categorisation of patients as <50% responders whenever only qualitative descriptions of seizure improvements were available [38]. When we examined duration of seizure freedom (with the inclusion of the RP cohort, 1 of whom reported seizure freedom at last follow-up), 16.5% reported seizure freedom for at least one 3-month study interval, 15/109 (13.8%) for at least one 6-month study interval, and 7/109 (6.4%) for 12 months of consecutive study intervals. 12/109 (11.0%) reported seizure freedom at some stage which persisted until respective study end-points. This rate assumes that those who withdrew consent but continued BRV treatment, and those for whom data were unavailable did not achieve seizure freedom, and so is likely conservative. Additionally, due to the cross-sectional study design it is possible that other periods of seizure freedom (e.g. from months 4 to 10) were missed.

On 3 measures of epilepsy drug-resistance - number of previous ASMs, number of ASMs at last available follow-up, and BRV maintenance dosage - mean average values of the TP and RP cohorts combined were in all cases numerically lower for ≥50% responders than for the rest of the cohort, but this reached statistical significance only in the case of ≥50% responders taking fewer ASMs at last follow-up (mean=1.9, range=1 to 3) than the rest of the cohort (mean=2.4, range=1-5), p = .013. Other differences may have reached statistical significance with larger sample size and higher power. These data suggest that those with better responses to BRV may simply represent a less drug-resistant subgroup. Nonetheless, ≥50% responders had historically trialled on average 4.7 previous ASMs, which still fulfilled the ILAE criteria for DRE [64], thus exemplifying the potential of BRV to considerably reduce seizure burden even among those with refractory epilepsy.

Seizure frequency category changes (e.g. changes from weekly to monthly seizures) were examined to gauge clinically meaningful change. Around one third (31.4%) of patients reported category improvements from baseline to last follow-up, whilst 44.2% remained in the same category and 24.4% worsened. Although our category deterioration rate was similar to the 20.8% of a comparable study [38], their category improvement rate was notably higher, at 56.1%. This is likely explained, however, by their shorter final follow-up period of 3 months compared to ours which was predominantly 6 months (with rates corrected accordingly) and which allowed more time for seizure recurrence.

Changes among the TP cohort to average monthly seizure frequency from baseline were as follows: Focal aware seizures/month showed significant reduction at 3 months, and remained unchanged at 6, 12 and 18 months. Focal impaired awareness seizures/month showed no significant change at any follow-up point. There was a significant monthly reduction in tonic-clonic seizures (both focal and generalised onset) at 12 months, but not at 3, 6 or 18 months. For all seizure types combined, there was a significant reduction in seizures/month at 3 months, but not at 6, 12, or 18 months. Significant improvements emerging in the first 3 months of treatment before tapering off were also seen by others [41], and could be explained by the well-known 'honeymoon period' phenomenon that is common in DRE, whereby a strong initial response to a newly-introduced ASM is followed by the gradual return to previous seizure frequency [41,66]. Analyses of seizure frequency changes from baseline to last follow-up included the TP and RP cohorts. When only seizures recorded during last available follow-up period were counted, only tonic-clonic seizures showed significant reductions, p = .045 (although median values did not differ). Of the subgroup of patients prone to tonic-clonic seizures (recorded either at either baseline or last FU) (N=36), tonic-clonic seizures/month had decreased in the majority of patients (21/36, 58.3%), with 9 (25.0%) achieving complete tonic-clonic seizure freedom by last available FU. When all seizures recorded from baseline to last follow-up were counted, monthly seizure frequency reduced from 5.0 at baseline to 4.3 at last follow-up - a 13.3% decrease - although not significant, p > .05. Villanueva et al [36], who included similar analyses, reported much greater seizure reductions (36.0% mean and 50.7% median) than ours, however this was likely due to methodological differences between the two studies: ours derived baseline seizure frequencies from the 3 months preceding BRV commencement regardless of seizure activity during this time, in order to limit retrospective recall bias and to be consistent in the baseline measurements. Villanueva et al, in instances where patients had recorded no seizures during the 3-month period, extended their baseline period to 12 months. An alternative approach, evading issues involved in defining 'baseline seizure frequency', was recently demonstrated by a novel time-based analysis which instead measured the number of days until patients reached seizure counts equivalent to in the 3 months preceding BRV initiation [39].

4.3 Tolerability & Safety

We investigated tolerability and safety of BRV via reports of treatment-emergent adverse events (TEAEs) and of TEAE-related BRV withdrawal. At least one TEAE was experienced by 91.7% patients with a median of 4 TEAEs per patient. Whilst this ≥1 TEAE rate was notably higher than in various retrospective studies (e.g. 36.9% [38]; 39.8% [36]), it was similar to rates derived from prospective data (e.g. 78.0% [43]; 84.5% [32]; 84.4% [35]; 88.8% [67]). The discrepancies across studies' TEAE rates are likely in-part attributable to methodological differences in prospective vs retrospective data collection. Differences in reportable AE criterion are also important, with some studies, such as our own, including all TEAEs *possibly* related to BRV, and others limiting AE data reporting to events *probably* and definitely related to BRV treatment. The majority (63.6%) of TEAEs reported throughout our study emerged within the first 3 months of treatment. Of all TEAEs, 58.4% were persistent, 5.3% intermittent, and 36.2% transient. The majority (60.1%) of the transient side effects had resolved within the first 6 months of treatment. These data suggest early onset and early resolution of many side effects.

The most frequently reported TEAEs were fatigue, irritability and depression/low mood, reported at least once by 30.3%, 29.4% and 28.4% of patients, respectively, and persistently by 19.3%, 16.5% and 21.1% of patients, respectively. These were also cited as most frequent in many other similar studies [36,38,39,43,44]. Permanent discontinuation of BRV due to TEAEs alone, or due to both TEAEs and lack of efficacy occurred in 30 patients i.e. in 30.0% of those reporting TEAEs, or 27.5% of the whole cohort. This was higher than in earlier literature [12,14,36,37], and may be attributable to the absence of any patient pre-selection for the BRIVEST study. Nonetheless, that less than one third of those reporting TEAEs consequently withdrew BRV treatment suggests that side effects experienced were relatively tolerable. Among those who withdrew BRV, the most frequent TEAE were depression/low mood (50.0%), irritability (43.3%), fatigue (30.0%) and anger (30.0%).

Psychiatric adverse events (PAEs) – changes in mood, anxiety and behaviour – were of particular interest in this study. At least one PAE was reported by 57.8% of patients. More than half of this subgroup (54.0%) had known histories of psychiatric comorbidity. The most frequently reported PAEs were irritability (29.4%), depression/low mood (28.4%), and anger (18.3%). Suicidal ideation and suicidal attempt were tracked closely: 11 patients reported suicidal ideation related to, or possibly related to BRV, including 1 case of attempted suicide. Nine of 11 patients had a history of depression. BRV treatment was withdrawn in 5/11 patients. In light of our high rate of reported suicidal ideation (10.1%), and of research indicating a higher prevalence of depression among those with DRE compared with the general epilepsy population [68], we investigated possible relationships between DRE and the reporting of suicidal ideation, however no significant associations were detected. The exact mechanisms underpinning the psychiatric side effects of BRV remain unclear, however they likely implicate the same systems associated with the psycho-behavioural profile of LEV, such as the serotonergic and GABA systems [41,69].

Psychiatric changes over time were tracked using 3 questionnaires of depression, anxiety and quality of life. For the TP cohort, significant increases in QoL scores from baseline indicated improved QoL over time, which echoed the findings of two LTFU studies [32,35]. Such observations could be attributable to better seizure control and/or fewer side effects, although it is also possible that those with better QoL before BRV initiation would be more resilient to side effects and would continue treatment longer, thus weighting mean scores towards higher QoL. Changes to QoL scores in the RP cohort were not significant, an unsurprising result given that questionnaires were first completed at least 6 months into treatment, likely missing any BRV-related changes to baseline QoL. Depression and anxiety scores remained stable over time for both cohorts, suggesting that BRV treatment did not adversely affect baseline levels of either condition. Accordingly, one would expect depression and anxiety reporting to be associated with pre-existing depression and anxiety. Indeed, suicidal ideation and increased anxiety were reported at significantly higher rates in those with histories of psychiatric comorbidities compared to those without (although depression was not).

4.4 Previous Levetiracetam Exposure

With more patients making a direct switch from LEV to BRV in the hope of superior tolerability, and with controlled comparative trials of BRV versus LEV lacking, treatment outcomes according to prior LEV exposure are of great interest. In our cohort, 64.6% of the previously LEV-exposed subgroup had withdrawn LEV due only to side effects, 20.2% due only to lack of efficacy, and 10.1% for both reasons (5.1% unknown). Overall, BRV efficacy did not differ according to LEV history: from baseline to last available FU there were no significant differences in either the ≥50% responder rates or changes to average monthly seizure frequency of LEV-

exposed patients and LEV-naïve patients. Although this was in line with recent research [38,65], various other studies have identified reduced seizure control in LEV-exposed versus LEV-naive patients [35,36,39,40]. These studies often noted higher numbers of previous and concomitant ASMs and higher baseline seizure frequency among their LEV-exposed subgroups, suggesting that they might simply represent a more drug-resistant subpopulation, meaning failure to respond to LEV should not necessarily preclude BRV treatment. This is further supported by findings of reduced BRV efficacy among those with previous exposure to a variety of ASMs other than LEV [49], and of generally better responses in those with fewer previous ASMs [31,70].

In terms of tolerability, history of LEV intolerance (here defined as LEV withdrawal due to side effects) did not predict any of the following measures of BRV tolerability: emergence of at least one TEAE on BRV, BRV withdrawal for any reason, or BRV withdrawal due to side effects. It did, however, predict reporting of unsteadiness and of fatigue on BRV. Throughout our study, 25 patients offered spontaneous comparisons of their experiences with BRV and LEV. Despite limited power, it is worth noting that among them 64.0% described BRV tolerability as 'significantly better', with almost all improvements relating to mood, behaviour and/or energy levels. This was in line with a recent review reporting improvement in behavioural and psychiatric side effects in 66.6% patients switching from LEV to BRV [48]. Unlike LEV, BRV has no negative modulatory effect on AMPA receptors, and it has been postulated that this may underlie the more favourable psychotropic profile of BRV [26-28]. Overall, our findings add to the body of literature supporting BRV as a promising alternative for those intolerant of LEV, with comparable efficacy and less severe TEAE burden [28,36,37,43-45,47,48].

4.5 Patients with Histories of Psychiatric Comorbidities

Psychiatric comorbidity rates among PWE are disproportionately high compared with the general population [1] and many established ASMs, including LEV, have the propensity to exacerbate existing conditions or cause PAEs *de novo* [48,53]. Given the shared mechanisms of BRV and LEV, it was important to characterise the tolerability profile of BRV among the psychiatrically vulnerable. Among those with histories of psychiatric comorbidities (n=52), the most frequently reported TEAEs were irritability (38.5%), depression/low mood (36.5%), and fatigue (36.5%). The rate of reporting at least one TEAE did not differ between those with and without a history of psychiatric comorbidity, however those with histories of psychiatric comorbidities reported headache, suicidal ideation and increased anxiety at significantly higher rates than those without (29.8% vs. 7%; 19.2% vs. 1.8%; and 23.1% vs. 1.8%, respectively). Closer inspection revealed that the reporting of suicidal ideation was significantly and specifically associated with a history of depression. Rates of reported depression, anxiety and psychosis were not similarly associated with specific previous histories of depression, anxiety or psychosis, respectively. On the whole, our findings support those of other studies [36,43,47] indicating that patients with histories of psychiatric comorbidities are not at increased risk of general BRV intolerability, although particular attention should be given to anxiety levels among this subgroup, and to suicidal ideation specifically among those with histories of depression.

4.6 Patients with Learning Disabilities

The limited literature concerning BRV tolerability among those with learning disabilities (LD), including those with developmental and epileptic encephalopathies (DEE), largely suggests BRV is similarly well-tolerated among those with and without LD [36,38,43,55,56], including among those with developmental and epileptic encephalopathies (DEE) [71] - a conclusion echoed in our own findings, which showed no difference between rates of reporting at least 1 TEAE in those with and without LD. The most commonly reported TEAEs in our LD subgroup were anger (40.0%) and fatigue (33.3%). Anger was the only specific side effect reported at an elevated rate in this subgroup (40.0%) compared with the rest of the cohort (14.9%), perhaps relatable to the increased aggression in LD reported elsewhere [43,55].

4.7 Patients of Older Age

With epilepsy now among the most common neurological disorders for a growing population of older adults [57], we also considered BRV tolerability among those of older age. This did not differ between those over and under 65 years of age, based on rates of ≥ TEAE, which aligned with a similar subgroup comparison [36]. Among our older age subgroup, fatigue was the most commonly reported TEAE (30.0%). Similarly, a pooled analysis of Phase III study data [72] reported somnolence among the most common TEAEs in this subgroup.

We found light-headedness to be the only side effect reported significantly more frequently (20.0%) in older versus younger adults (1.0%). Our data support a useful therapeutic role of BRV for epilepsy in older age. Although there was not scope for the present study to investigate BRV treatment outcomes in children and adolescents, it is important to note that the growing literature thus far supports BRV as a safe and effective ASM in this subpopulation [73, 74, 75].

4.8 Study Limitations

This was a single-centre study with a relatively small sample size and limited power, although this reflected the prescribing of BRV soon after its introduction into the hospital formulary, and was in keeping with similar studies (e.g. 42,44). Our observational design prevented the standardisation of BRV dosing and concomitant ASM usage, including regimes for BRV titration and LEV-BRV switches, all of which were at the discretion of the treating clinician. There may be some other confounding relations in the data too (omitted variable bias) that we could not reasonably account for, limiting the certainty of conclusions concerning the efficacy and tolerability of BRV *per se*. The lack of randomisation and blinding may also have introduced some bias. Although allowing for a truly consecutive, unselected and representative patient cohort, and diminishing the risk of selection bias, the inclusion of retrospective data collection (alongside the predominantly prospective follow-up) brought with it certain constraints: follow-up timing varied across patients, and data capture from medical records and patient interviews risked omission of some information. 'In addition, with the information available to us it was not possible to comment with certainty on the poor retention outcomes in this retrospective cohort, which may have been partly due to methodology (i.e. the way in which this cohort was defined), but also due to factors such as tolerance for side effects, and severity of epilepsy. Also, whilst the 3-month retrospective baseline period ensured methodological consistency and limited recall inaccuracies associated with longer retrospective run-in periods, it is possible that important periods of seizure activity - or lack thereof - were not captured, in turn leading to inaccurate impressions of decreased or increased seizure frequency over time. Further, multiple statistical tests - informed by clinically-important questions arising from existing literature - were performed to describe the data and thus there is the possibility of some chance sample idiosyncratic features which might not replicate. In particular, owing to the heterogeneous patient pool, findings regarding specific subgroups must be interpreted with caution. Finally, it has to be highlighted that a large proportion of recruitment took place near the start of the Covid-19 pandemic, and as such it is difficult to disentangle BRV-related and lockdown-related PAEs, of which emerging UK-based research shows there are many [76,77]. This may go some way in explaining our higher TEAE rates compared to those of earlier studies.

4.9 Conclusions

The BRIVEST study adds to a growing body of literature derived from the 'real-life' and 'real-time' investigation of BRV. Although variations in methodology make direct comparisons to other studies, findings here are in line with previous RCTs and post-marketing studies [9-14,28,36–44] characterising BRV as an effective ASM with good efficacy and tolerability. Our results show that both significant seizure reduction and seizure freedom can be achieved with BRV in patients with highly refractory epilepsy. Consistent with several similar studies [36,38,39,43,44], fatigue, irritability, and depression/low mood were the most frequently reported side effects. The overall AE profile of BRV was relatively benign, with less than a third of those reporting side effects withdrawing because of them. Further, questionnaire data suggested that overall anxiety and depression levels remained stable over time, whilst quality of life in fact improved. Efficacy and tolerability for BRV did not differ between those who had and had not previously failed LEV treatment, indicating BRV could be a viable treatment alternative for patients with previously suboptimal responses to LEV. Similarly, tolerability profiles of those with comorbid learning disabilities, and those of older age, did not greatly differ from the rest of the cohort. There was, however, an increased risk of suicidal ideation and heightened anxiety on BRV among those with histories of psychiatric comorbidity. The subgroups considered in the present study are often excluded from epilepsy-related RCTs, and as such it is important that treatment responses among these groups continue to be investigated at larger scales. Greater statistical power would also allow for more complex subgroup analyses of, for example, BRV treatment outcomes in individuals who traverse multiple vulnerable patient subpopulations.

Declaration of Competing Interest

The study was designed and set up as an Independent Investigator Initiated Study by Katarzyna Sieradzan and hosted by North Bristol NHS Trust. UCB provided funding for the study including the salaries of the Research Staff (except for Katarzyna Sieradzan and Paul White who did not personally receive any funding from UCB). No UCB personnel were involved in study design, data collection, data analysis, or preparation of the manuscript. Sophie Naddell, Megan Manuel, Rebecca Cavill and Paul White have no past UCB affiliations to declare. Katarzyna Sieradzan has acted as local PI on multicentre clinical trials funded by UCB and LivaNova, and received advisory board and speaker honoraria from Eisai and UCB, and an educational grant from Eisai.

Ethics Approval

The study protocol, amendments, and patient documents were approved by the Yorkshire & the Humber - Leeds West Research Ethics Committee (this body considers research projects involving LD patients nationally) and by the Health Research Authority (HRA) and Health and Care Research Wales (HCRW). Data collection, storage and management were compliant with Good Clinical Practice and in accordance with the Declaration of Helsinki.

Consent to Participate

Informed consent was not required from those who withdrew BRV treatment before study start, due to use of anonymised retrospective data from routine clinical care. Informed consent was obtained from all other patients, and for those unable to give their informed consent, consenting involved their personal and professional consultees and/or legal representatives according to the process approved by the Ethics Committee.

Availability of Data and Material

Anonymized data and materials can be shared at the request of qualified investigators.

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APPENDICES

Appendix A. Inclusion and Exclusion Criteria for Study Eligibility

Inclusion Criteria	*Exclusion Criteria*
• Clinical diagnosis of epilepsy. • Clinical decision made, prior to study enrolment, to prescribe BRV as part of patient's normal clinical care. • BRV treatment was commenced after 24/05/2016 when it became available on North Bristol Trust formulary. • Patient able to provide full informed consent, or: Parent or carer responsible for the patient's epilepsy care able to provide consent on the patient's behalf. • Patient aged ≥18 years.	• Aged < 18 years old. • Patient (or carer(s)) unable to keep a reliable record of seizures. • Very frequent daily seizures that are impossible to record with reasonable accuracy. • Unable to attend follow up appointments or be able to complete study questionnaires.

Appendix B. Complete List of TEAEs

Side effect	N (%)	N (%) persistent	N (%) intermittent	N (%) transient	Follow-up at which onset most commonly reported (mode)	If transient, follow-up at which resolution most commonly reported (mode)
Fatigue	33 (30.3)	21 (19.3)	4 (3.7)	8 (7.3)	3m	12m
Irritability *	32 (29.4)	18 (16.5)	2 (1.8)	12 (11.0)	3m	6m
Depression *	31 (28.4)	23 (21.1)	1 (0.9)	7 (6.4)	3m	6m
Increase in seizure frequency	31 (28.4)	25 (22.9)	3 (2.8)	3 (2.8)	3m	12m
Sleep disturbance	27 (24.8)	13 (11.9)	4 (3.7)	10 (9.2)	3m	6m
Anger *	20 (18.3)	14 (12.8)	1 (0.9)	5 (4.6)	3m	6m
Somnolence / sedation	20 (18.3)	11 (10.1)	4 (3.7)	5 (4.6)	3m	12m
Headache	19 (17.4)	11 (10.1)	1 (0.9)	7 (6.4)	3m	3m
Rapidly fluctuating mood *	18 (16.5)	9 (8.3)	1 (0.9)	8 (7.3)	3m	12m
Nausea	18 (16.5)	7 (6.4)	0 (0.0)	11 (10.1)	Baseline	3m
Unsteadiness	17 (15.6)	10 (9.2)	0 (0.0)	7 (6.4)	Baseline	3m
Memory problems	17 (15.6)	13 (11.9)	0 (0.0)	4 (3.7)	3m	6m
Confusion / mental slowing	17 (15.6)	7 (6.4)	1 (0.9)	9 (8.3)	Baseline	3m
Dizziness	17 (15.6)	9 (8.3)	0 (0.0)	8 (7.3)	Baseline	-
Aggression *	13 (11.9)	8 (7.3)	0 (0.0)	5 (4.6)	3m	6m
Increased anxiety *	13 (11.9)	9 (8.3)	0 (0.0)	4 (3.7)	3m	3/6/12/24m
Gastro-intestinal disturbance	13 (11.9)	6 (5.5)	1 (0.9)	6 (5.5)	Baseline	6m
Suicidal ideation *	11 (10.1)	6 (5.5)	0 (0.0)	5 (4.6)	3m	6m
Pins & needles / numbness	10 (9.2)	3 (2.8)	2 (1.8)	5 (4.6)	Baseline	12
Weight loss	9 (8.3)	6 (5.5)	0 (0.0)	3 (2.8)	Baseline	6m
Depersonalisation / abnormal thoughts *	8 (7.3)	5 (4.6)	0 (0.0)	3 (2.8)	Baseline	3m

Limb / joint pain	8 (7.3)	3 (2.8)	0 (0.0)	5 (4.6)	3m	3m
Changes to menstrual period	7 (6.4)	3 (2.8)	0 (0.0)	4 (3.7)	6m	12m
Constipation	7 (6.4)	5 (4.6)	0 (0.0)	2 (1.8)	3m	12m
Word finding difficulties	7 (6.4)	1 (0.9)	0 (0.0)	6 (5.5)	6m	24m
Slurred speech	6 (5.5)	3 (2.8)	0 (0.0)	3 (2.8)	Baseline	3m
Frequent need to pass urine	4 (3.7)	1 (0.9)	0 (0.0)	3 (2.8)	3m	6/12/18m
Double vision	4 (3.7)	1 (0.9)	1 (0.9)	2 (1.8)	Baseline	3/6m
Skin irritation	3 (2.8)	1 (0.9)	0 (0.0)	2 (1.8)	Baseline/3/6m	3/12m
Breathlessness	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	Baseline	3m
Tremor	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	Baseline/6/18m	12m
Dehydration / increased thirst	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	Baseline/6/12m	18
Loss of sex drive	3 (2.8)	3 (2.8)	0 (0.0)	0 (0.0)	18m	-
Migraines	3 (2.8)	2 (1.8)	1 (0.9)	0 (0.0)	18m	-
Paranoia *	3 (2.8)	1 (0.9)	0 (0.0)	2 (1.8)	3m	6m
Night sweats	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	3/6/12m	6m
Concentration difficulties	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	Baseline	18m
Weight gain	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	3/30/42m	6m
Light-headedness	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	Baseline	6m
Lack of motivation *	3 (2.8)	3 (2.8)	0 (0.0)	0 (0.0)	6m	-
Increased focal aware seizures	3 (2.8)	2 (1.8)	0 (0.0)	1 (0.9)	6/18/26m	42m
Ringing in ear	2 (1.8)	1 (0.9)	0 (0.0)	1 (0.9)	6/12m	12m
Increased contusion	2 (1.8)	1 (0.9)	0 (0.0)	1 (0.9)	3/24m	6m
Visual disturbance	2 (1.8)	1 (0.9)	0 (0.0)	1 (0.9)	6/12m	18m
Vomiting	2 (1.8)	1 (0.9)	0 (0.0)	1 (0.9)	Baseline/6m	12m
Reduced 'warning' before seizures	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)	18/42m	-
Hallucinations *	2 (1.8)	0 (0.0)	0 (0.0)	2 (1.8)	Baseline/3m	3/6m
Extremities of mood *	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)	6/12m	-
Dry mouth	2 (1.8)	2 (1.8)	0 (0.0)	0 (0.0)	Baseline/24m	-
Psychosis *	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	3m	-
Tooth grinding / cheek biting	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	Baseline	-
Cold hands and feet	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	3m	6m
Increased pain sensitivity	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	Baseline	3m
Loss of appetite	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	30m	-
Vivid dreams	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	30m	-
More violent seizure clusters	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	42m	-
Increase in heart rate & blood pressure	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	Baseline	6m
Increased emotional sensitivity *	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	Baseline	6m
Argumentativeness *	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)	Baseline	6m
Hair loss	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	3m	-
Chest pains	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	3m	-
General malaise	1 (0.9)	1 (0.9)	0 (0.0)	0 (0.0)	3m	-

Note: Asterisks (*) indicate psychiatric AEs.

Appendix C. Beck's Depression Inventory (BDI) Scores

		True Prospective	Retrospective-Prospective
Baseline	N	35	23
	Mean (SD)	11.8 (9.7)	14.6 (11.0)
	Median (Q1, Q3)	10.0 (5.0, 16.0)	11.0 (8.0, 16.0)
3-month FU	N	40	-
	Mean (SD)	12.3 (11.9)	-
	Median (Q1, Q3)	9.0 (3.8, 17.8)	-
6-month FU	N	42	23
	Mean (SD)	10.8 (10.0)	15.5 (11.6)
	Median (Q1, Q3)	8.0 (4.0, 17.0)	12.0 (5.5, 25.0)
12-month FU	N	29	18
	Mean (SD)	10.1 (9.4)	15.1 (10.6)
	Median (Q1, Q3)	7.0 (4.0, 15.0)	13.0 (6.0, 26.0)
18-month FU	N	15	-
	Mean (SD)	11.6 (7.8)	-
	Median (Q1, Q3)	10.0 (6.0, 18.0)	-

Appendix D. Beck's Anxiety Inventory (BAI) Scores

		True Prospective	Retrospective-Prospective
Baseline	N	36	23
	Mean (SD)	12.8 (11.0)	14.9 (15.8)
	Median (Q1, Q3)	8.5 (3.0, 22.8)	10.0 (3.5, 19.5)
3-month FU	N	41	-
	Mean (SD)	11.7 (11.9)	-
	Median (Q1, Q3)	7.0 (3.0, 16.0)	-
6-month FU	N	42	23
	Mean (SD)	12.4 (12.3)	16.3 (11.3)
	Median (Q1, Q3)	9.0 (3.3, 17.5)	14.0 (8.5, 23.0)
12-month FU	N	29	20
	Mean (SD)	13.1 (12.1)	15.9 (9.8)
	Median (Q1, Q3)	12.0 (5.0, 20.0)	12.5 (8.0, 26.5)
18-month FU	N	15	-
	Mean (SD)	12.5 (10.2)	-
	Median (Q1, Q3)	9.0 (6.0, 20.5)	-

Appendix E. Quality of Life in Epilepsy (QOLIE-31-P v.2) Scores

		True Prospective	Retrospective-Prospective
Baseline	N	35	24
	Mean (SD)	55.3 (13.7)	59.3 (16.4)
	Median (Q1, Q3)	55.1 (48.0, 65.3)	63.1 (43.6, 69.1)
3-month FU	N	41	-
	Mean (SD)	59.5 (19.7)	-
	Median (Q1, Q3)	66.4 (51.3, 70.8)	-
6-month FU	N	42	23
	Mean (SD)	63.8 (17.2)	58.3 (19.5)
	Median (Q1, Q3)	66.2 (55.2, 76.9)	57.2 (44.7, 75.4)
12-month FU	N	29	18
	Mean (SD)	66.7 (16.4)	61.2 (14.4)
	Median (Q1, Q3)	73.75 (57.0, 76.8)	59.1 (52.6, 72.1)
18-month FU	N	15	-

	Mean (SD)	67.7 (15.2)	-
	Median (Q1, Q3)	71.3 (57.0, 76.7)	-

Supplementary Material

To complement '3.4.3 Monthly Seizure Frequency':

Among the TP cohort, analyses (n=45) revealed a significant reduction in focal aware seizure frequency at 3 months (n = 46, mean = 9.6, SD = 41.8, median = 0.0, IQR = 3.1) compared to at baseline (n=52, mean = 26.4, SD = 118.6, median = 0.0, IQR = 4.8), z = -2.5, p = .013, with a small effect size, r = .26. Here, seizure frequency had reduced in 15 subjects, remained unchanged in 26 and increased in 4. Changes to focal aware seizure frequency at 6, 12 and 18 months were not significant, with z = -1.6, -1.8, and -1.2 respectively, and p = .12, .074 and .25 respectively. For focal impaired awareness seizures, there were no significant changes from baseline seizure frequency, with z = -.42, -.54, -.23 and -.45, and p = .68, .59, .82 and .66, at 3, 6, 12, and 18 months respectively. In the case of tonic clonic seizures, a significant reduction was detected at 12 months (n = 36, mean = .55, SD = 2.1, median = 0.0, IQR = .13) compared to at baseline (n=59, mean = .85, SD = 2.5, median = 0.0, IQR = .33), z = -2.0, p = .042, with a small effect size, r = .24. Here, seizure frequency had reduced in 10 subjects, remained unchanged in 23, and increased in 3. Changes were not significant at 3, 6 or 18 months, with z= -1.5, -1.9, and -1.6, and p = .13, .061, and .11, respectively. When all seizure types were grouped together, analyses revealed a significant reduction in seizure frequency at 3 months (n = 53, mean = 17.4, SD = 47.2, median = 3.0, IQR = 12.8) compared to at baseline (n=59, mean = 51.4, SD = 152.1, median = 5.0, IQR = 18.7), z = -2.2, p = .031, with a small effect size, r = .21. Here, seizure frequency had reduced in 28 subjects, remained unchanged in 10, and increased in 15. Changes at 6, 12 and 18 months were not significant, z = -1.5, -.74, and -.14 respectively, and p = .13, .46 and .89, respectively.

Data from the TP and RP cohorts were combined for analyses of changes to mean seizures/month from baseline to last available follow-up. All subjects completing at least one prospective study follow-up, and with eligible data, were included. Seizure frequency at last available follow-up was considered in two formats: firstly, total number seizures recorded throughout the entirety of the prospective follow-up period, divided by the number of months of follow-up; and secondly, total number of seizures recorded throughout the last available follow-up period alone (e.g. 6 to 12 months) divided by the number of months in this period (e.g. 6). For the former, medians of the mean average monthly seizure frequency decreased by 13.3%, from 5.0 at baseline to 4.3 at last available follow-up, however this reduction did not reach statistical significance, p = .35. For the latter, changes from baseline were not significant in the case of focal aware, focal impaired awareness or all seizure types, with z = -0.73, -1.0, and -.31 respectively, and p = .47, .32 and .75, respectively. For tonic-clonic seizures, however, a significant reduction in seizure frequency (n=85) was observed from baseline (n=93, mean = .91, SD = 2.4, median = 0.0, IQR = .67) to last available follow-up (n = 85, mean = .54, SD = 1.6, median = 0.0, IQR = .33), z = -2.0, p = .045, with a small effect size, r = .15. Here, tonic-clonic seizure frequency decreased in 21 subjects, remained the same in 51, and increased in 13. Reductions in tonic-clonic seizures were explored further by excluding those who did not record this seizure type at either baseline or at last available FU: Of the 36 subjects who completed at least one prospective FU and who did record this seizure type at either baseline or last available FU, 21/36 (58.3%) subjects showed a decrease in tonic-clonic seizures/month from baseline to last available follow-up. 2/36 (5.6%) subjects showed no change, whilst 13/36 (36.1%) showed an increase in monthly frequency. 9 subjects (42.9% of the 21 who improved, 31.0% of the 29 with tonic-clonic seizures recorded at baseline, or 25.0% of the 36 recording tonic-clonic seizures at either follow-up) had achieved complete tonic-clonic seizure freedom at last available FU.