A 12-MONTH NONINTERVENTIONAL OBSERVATIONAL MULTINATIONAL STUDY TO EVALUATE EFFECTIVENESS, TOLERABILITY, AND QUALITY OF LIFE OF BRIVARACETAM ADJUNCTIVE THERAPY IN EARLIER TREATMENT LINES IN ADULT PATIENTS WITH HISTORY OF PARTIAL-ONSET SEIZURES IN DAILY CLINICAL PRACTICE

REPORT EP0103

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BELGIUM

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STUDY INFORMATION

Title	A 12-Month Noninterventional Observational Multinational Study to Evaluate Effectiveness, Tolerability, and Quality of Life of Brivaracetam Adjunctive Therapy in Earlier Treatment Lines in Adult Patients with History of Partial-Onset Seizures in Daily Clinical Practice
Study Number	EP0103
Date of last version of Study Report	10 Oct 2024
European (EU) Post-Authorization Study (PAS) register number (if applicable)	EUPAS41206
Research question and objectives	The primary objective of the study was to evaluate the effectiveness of brivaracetam in earlier treatment line combinations in patients with partial-onset seizures with or without secondary generalization for approximately 12 months of treatment.
Countries of study	Germany, Italy, Spain, France, Canada
Author(s)	[redacted]

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2 ABSTRACT

Title

A 12-Month Noninterventional Observational Multinational Study to Evaluate Effectiveness, Tolerability, and Quality of Life of Brivaracetam Adjunctive Therapy in Earlier Treatment Lines in Adult Patients with History of Partial-Onset Seizures in Daily Clinical Practice

Keywords

Brivaracetam, Epilepsy, Europe and Canada, Real-world practice, UCB, Noninterventional study (NIS), Quality of life, Work productivity, Partial-onset seizures (POS), Earlier treatment lines, Treatment satisfaction

Rationale and background

EP0103 was a postmarketing, multinational, observational, prospective NIS to evaluate effectiveness, tolerability, and impact on patient quality of life of adjunctive brivaracetam therapy in earlier treatment line combinations in adult patients with history of POS.

This NIS was designed to close this existing data gap focusing on evidence for brivaracetam adjunctive therapy and on exploring possible predictions of response in earlier treatment line combinations.

Research question and objectives

The primary objective of the study was to evaluate the effectiveness of brivaracetam in earlier treatment line combinations in patients with POS with or without secondary generalization for approximately 12 months of treatment.

The secondary objective of this study was to assess the effectiveness of brivaracetam treatment in earlier treatment line combinations.

Other objectives of this study were to assess the health outcomes under brivaracetam in earlier treatment line combinations, to evaluate the speed of onset and sustained effectiveness of brivaracetam in clinical practice, to describe patient profiles for brivaracetam in earlier treatment line combinations, to assess the safety and tolerability profile (including behavioral adverse events [AEs]) of brivaracetam in earlier treatment line combinations, and to assess Baseline predictors associated with brivaracetam effectiveness in earlier treatment line combinations.

Study design

This was a postmarketing, multinational, observational, prospective NIS conducted at approximately 100 sites in Europe (Germany, Italy, Spain, and France) and Canada.

Each patient was followed for approximately 12 months with 5 study visits as per standard clinical practice. Apart from requesting completion of patient-reported questionnaires (which was a voluntary decision by the patient), no additional clinical procedures were applied except as required in the standard practice of medicine.

Patients had the option of completing the questionnaires and reporting seizure frequency using the Helpilepsy application for Visits 1 to 5. For those patients who did not use the Helpilepsy application, seizure information and patient-reported outcomes (PROs) were collected via paper questionnaires and based on the medical chart information.

Setting

This study was conducted in Germany, Italy, Spain, France, and Canada.

Patients and study size, including dropouts

Taking into consideration some drop out during the study period, originally a sample of 600 eligible patients was planned for the study to result in 500 patients being included in the Safety Set (SS).

Due to unforeseen delays in enrollment, including the coronavirus 2019 (COVID-19) pandemic, the sample size was reduced from 600 patients to 400 enrolled patients in Protocol Amendment 2.0.

Variables and data sources

Effectiveness variables

The primary variable in this study was seizure freedom for at least 6 consecutive months over the 12-month observation period.

The secondary variables in this study included the following at 3, 6, 9, and 12 months: brivaracetam retention, seizure freedom, POS frequency (also at Baseline), Change (absolute and percent) in POS frequency from Baseline, and response rate (number and percentage of patients achieving reduction of ≥50% from Baseline) based on percent change in POS frequency. Secondary variables also included discontinuation of brivaracetam due to lack of effectiveness and time to discontinuation of brivaracetam treatment.

Other effectiveness variables were self-reported seizure frequency and time to first seizure after first dose of brivaracetam.

Health outcome variables

Health outcome variables included:

- Patient Global Impression of Change (PGIC) rating at 3, 6, 9, and 12 months
- Clinical Global Impression of Change (CGIC) rating at 3, 6, 9, and 12 months
- Patient-Weighted Quality of Life in Epilepsy Inventory-10-P (QOLIE-10-P) total score at Baseline, 6, and 12 months
- Change in QOLIE-10-P total score from Baseline to 6 and 12 months
- Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) scores for each scale at Baseline, 3, 6, 9, and 12 months
- Change in TSQM-9 scores for each scale from Baseline to 3, 6, 9, and 12 months
- Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) scores for each scale at Baseline, 3, 6, 9, and 12 months
- Change in WPAI:GH scores for each scale from Baseline to 3, 6, 9, and 12 months
- Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) total score at Baseline, 6, and 12 months

- Change in NDDI-E total score from Baseline to 6 and 12 months
- Seizure Severity Questionnaire (SSQ) rating for questions 5 and 8 at Baseline, 3, 6, 9, and 12 months

Safety variables

Safety variables included incidences of treatment-emergent adverse events (TEAEs), behavioral TEAEs, serious TEAEs (including serious behavioral TEAEs), and study drug-related TEAEs (including behavioral TEAEs), as well as incidences of TEAEs and behavioral TEAEs leading to discontinuation, adverse events of special interest (AESI), incidence of prior antiepileptic drug (AED)-related AEs leading to discontinuation of respective AED, exposure to brivaracetam, and incidence of other safety relevant (OSR) information.

Results

Demographics and Baseline characteristics:

A total of 403 patients were enrolled at 62 sites across Germany (172 patients enrolled at 21 sites), Italy (110 patients enrolled at 19 sites), Spain (26 patients enrolled at 5 sites), France (87 patients enrolled at 13 sites), and Canada (8 patients enrolled at 4 sites). All 403 patients were included in the All Patients Documented Set, 392 (97.3%) patients were included in the SS, and 304 (75.4%) patients were included in the Per Protocol Set (PPS). Of the 392 patients in the SS, 298 (76.0%) completed the 12-month study period; 94 (24.0%) discontinued the study prematurely.

At Baseline, the mean (SD) age of all patients was 44.9 (17.4) years for the SS. Around half (52.0%) of patients were male. The majority (65.3%) of patients did not use the Helpilepsy application. The median time elapsed since first diagnosis of epilepsy for the SS was 8.37 years, and 175 (44.6%) patients had a time since first diagnosis of epilepsy of >10 years. The median percent of life with epilepsy was 21.68%.

Of the 392 patients in the SS, 381 (97.2%) patients reported any Baseline POS. Among these 381 patients, the median (Q1, Q3) 28-day Baseline POS frequency (based on the 3 months prior to Visit 1) was 2.00 (0.67, 4.00). Baseline POS with secondary generalization were reported by 143 (36.5%) patients. Among these 143 patients, the median (Q1, Q3) 28-day Baseline POS with secondary generalization frequency (based on the 3 months prior to Visit 1) was 0.67 (0.33, 1.00).

For the SS, the percentages of patients who had 1, 2, or 3 lifetime AEDs at brivaracetam initiation were 29.6%, 41.1%, or 23.7%, respectively. The median (Q1, Q3) number of lifetime AEDs was 2.0 (1.0, 3.0).

In the SS, 99.7% (391/392) of patients had any concomitant AEDs at brivaracetam initiation. The percentages of patients who had 1 or 2 concomitant AEDs at brivaracetam initiation were 61.5% and 32.9%, respectively. The median (Q1, Q3) number of concomitant AEDs at brivaracetam initiation was 1.0 (1.0, 2.0).

Effectiveness:

Primary variable:

- Of the patients who completed consecutive visits at least 6 months apart, 41.9% of patients in the SS and 42.2% in the PPS were seizure free for at least 6 consecutive months over the 12-month observation period.

Secondary variables:

- Overall, brivaracetam retention remained high throughout the study. At 12 months, 75.5% of patients in the SS and 77.0% of patients in the PPS remained on the adjunctive brivaracetam treatment.
- Seizure freedom throughout 12 months was achieved by 20.5% of patients in the SS and 19.9% of patients in the PPS.
- Median POS frequency decreased at all timepoints (1.67 at Visit 1 [Baseline], 0.57 at Visit 2 [Month 3], 0.31 at Visit 3 [Month 6], 0.20 at Visit 4 [Month 9], and 0.00 at Visit 5 [Month 12] for the SS).
- The median absolute reduction in all types POS frequency from Baseline was >0 at all timepoints and consistent over time (0.71 at Visit 2 [Month 3], 1.00 at Visit 3 [Month 6], Visit 4 [Month 9], and Visit 5 [Month 12] for the SS). The median percent reduction from Baseline was >0 at all timepoints (68.60% at Visit 2 [Month 3], 81.33% at Visit 3 [Month 6], 82.50% at Visit 4 [Month 9] for the SS) and was 100.00% at Visit 5 (Month 12) for the SS and the PPS.
- The number and percentage of patients with a response of ≥50% seizure reduction increased over time (56.0% at Visit 2 [Month 3], 68.1% at Visit 3 [Month 6], 68.7% at Visit 4 [Month 9] in the SS) with the highest percentage occurring at Visit 5 (Month 12) (75.7% in the SS; 77.6% in the PPS).
- Seventeen (4.3%) patients in the SS discontinued brivaracetam due to lack of efficacy, and 12 (3.9%) patients in the PPS discontinued brivaracetam due to lack of efficacy.
- Overall, 94 (24.0%) patients in the SS and 67 (22.0%) patients in the PPS discontinued brivaracetam.

Other effectiveness variables:

- For the patients using Helpilepsy to report seizures (n=134 for the SS; n=90 for the PPS), the median number of all types of seizures was 0.0 at all timepoints.
- The median time to first seizure in patients using Helpilepsy was 82.0 days in the SS and 143.0 days in the PPS.

Overall, effectiveness results were comparable between the SS and the PPS.

Health outcomes:

- For the CGIC, physicians reported any improvement in clinical condition over the past 4 weeks compared with Baseline (sum of minimal, much, and very much improvement) for 72.0% of patients in the SS at Month 12, while no change was reported for 19.7% of patients.

For the PGIC, 66.8% of patients in the SS reported any improvement at Month 12, while 26.1% reported no change.

- The change from Baseline in the QOLIE-10-P total score showed mean increases up to Month 12, indicating improvement in quality of life. A similar trend was observed in the epilepsy distress score.
- The observed TSQM-9 mean scores showed a trend of steady increase in all 3 domain score changes from Baseline over time, indicating improvement throughout the study in patient perceived effectiveness, convenience, and global satisfaction with initiation of adjunctive brivaracetam treatment.
- The observed WPAI:GH mean scores showed a decrease in scores from Baseline across all dimensions, indicating improved patient activity and work impairment, better productivity, and less work time missed over time upon initiating adjunctive brivaracetam treatment. Notably, some subscales were reported only by patients with a job.
- The observed NDDI-E total score showed small numerical decreases in median values from Baseline, suggesting a reduction in depressive symptoms.
- Per question 5 of the SSQ, the number and percentage of patients who reported the presence of cognitive effects (yes/no) after seizures decreased over time. In patients who had cognitive effects after seizures, the mean scores related to the frequency, severity, and bothersomeness of these cognitive effects tended to be slightly reduced over time. For question 8 of the SSQ, there was improvement through Month 6 in mean and median values. Mean values continued to slightly decrease and median values remained stable thereafter.

Overall, health outcomes were comparable between the SS and the PPS.

Safety:

- The median total daily dose at Visit 1 (Baseline) was 50.0mg/day in the SS, which then increased to 100.0mg/day for the remainder of the study (Visit 2 through Visit 5).
- Overall, 101 (25.8%) patients reported 215 TEAEs in the SS. The most common TEAE was fatigue (20 [5.1%] patients), followed by seizure (12 [3.1%] patients) and dizziness (12 [3.1%] patients).
- Twelve (3.1%) patients in the SS experienced 15 serious TEAEs. The most frequently reported serious TEAEs by preferred term (PT) were seizure (3 [0.8%] patients) and partial seizures with secondary generalization (2 [0.5%] patients). No other serious TEAEs were reported in more than 1 patient.
- Study drug-related TEAEs occurred in 54 (13.8%) patients in the SS. The most frequently reported PTs were fatigue (13 [3.3%] patients), dizziness (10 [2.6%] patients), somnolence (9 [2.3%] patients), and seizure (8 [2.0%] patients).
- There were 37 (9.4%) patients who experienced 68 TEAEs that led to brivaracetam discontinuation in the SS. The most frequently reported PTs that led to brivaracetam discontinuation were fatigue (9 [2.3%] patients), dizziness (9 [2.3%] patients), and seizure (8 [2.0%] patients).

- Behavioral TEAEs occurred in 12 (3.1%) patients in the SS. There was 1 (0.3%) patient who experienced a serious behavioral TEAE during the study (PT: irritability). Eleven (2.8%) patients experienced 13 study drug-related non-serious behavioral TEAEs (PTs: irritability [1.8%], aggression [0.5%], agitation [0.5%], affect lability [0.3%]). Five (1.3%) patients experienced 6 behavioral TEAEs that led to brivaracetam discontinuation (PTs: irritability [1.0%], aggression [0.3%], agitation [0.3%]). Overall, the most frequently reported behavioral TEAE was irritability (8 [2.0%] patients).
- One (0.3%) patient reported 1 pregnancy.
- There were no deaths during the study.

Overall, safety results were comparable between the SS and the PPS.

Discussion

The results of this NIS suggest that adjunctive brivaracetam is effective and well tolerated in real-world clinical practice when used in earlier treatment line combinations for patients with POS. Approximately 42% of patients in the SS were seizure free for at least 6 months within the study duration. In addition, patients benefitted from improved quality of life, better work productivity and reduced work impairment, less epilepsy distress, fewer cognitive effects after seizures, and reduced seizure severity. The outcomes of the study are consistent with the published results of clinical studies and other NIS, including the post-hoc analyses. The safety profile was in line with previous brivaracetam studies.

Marketing Authorization Holder(s)

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3 LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
AESI	adverse events of special interest
APD	All Patients Documented Set
BAE	behavioral adverse event
CDMS	clinical data management system
CGIC	Clinical Global Impression of Change
CI	confidence interval
COVID-19	coronavirus 2019
CRO	contract research organization
CYP	cytochrome P450
DEM	data evaluation meeting
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EOS	End of Study
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LEV	levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
NIS	noninterventional study
OSR	other safety relevant
PAS	post-authorization study
PDCF	Patient Data Consent Form
PGIC	Patient Global Impression of Change
POS	partial-onset seizures
PPS	Per Protocol Set
PRO	patient-reported outcome
PT	preferred term
QoL	quality of life
QOLIE-10-P	Patient-Weighted Quality of Life in Epilepsy Inventory-10-P
SAE	serious adverse event

SAP	statistical analysis plan
SAS	Statistical Analysis System
SmPC	Summary of Product Characteristics
SOC	system organ class
SS	Safety Set
SSQ	Seizure Severity Questionnaire
TEAE	treatment-emergent adverse event
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
WHODD	World Health Organization Drug Dictionary
WPAI:GH	Work Productivity and Activity Impairment Questionnaire: General Health

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5 STUDY PROTOCOL AMENDMENTS AND UPDATES

Number	Date	Amendment or update	Section of the protocol	Reason
1	17 Nov 2021	Amendment 1.0	Section 1: Background and rationale for the study	Added the 22 Mar 2020 approval of the oral brivaracetam formulations in patients ≥4 years of age in Canada.
			Section 5: Study design	Revised former text that stipulated that only Visits 2 and 4 could have been remote to state that all 5 study visits may have been remote (conducted via a call), if needed.
			Section 5.1.1: Visit 1: Baseline/first day of brivaracetam treatment	Revised the text stating that Visit 1 (Baseline) **will be** the patient's first day of brivaracetam treatment to state that Visit 1 **should be** the patients first day of brivaracetam treatment. Added text that the patient-reported questionnaires completed at Visit 1 (Baseline) were based upon the patient's prior treatments. Added text to note that for patients who were not using the Helpilepsy application and completed their visits remotely (via a call), questionnaires were not completed.
			Section 5.1.1: Visit 1: Baseline/first day of	Removed collection of race and ethnicity as part of the

Number	Date	Amendment or update	Section of the protocol	Reason
			brivaracetam treatment & Section 5.2 Schedule of activities	demographic data collected at Visit 1. Updated to consistently refer to "gender" as "sex."
			Section 5.1.1: Visit 1: Baseline/first day of brivaracetam treatment & Section 14.1 Patient data consent form	Revised to allow the signing of the PDCF to occur at the site or remotely (via mail), if it was necessary.
			Section 5.1.3 Visit 3: approximately 6 months & Section 5.1.5 Visit 5: approximately 12 months/End of Study	Added text to note that for patients who were not using the Helpilepsy application and completed their visits remotely (via a call), questionnaires were not completed.
			Section 5.2 Schedule of activities	Applied the following footnote: "This visit can be completed via a telephone call with the site" to all study visits. Revised the footnote describing questionnaires to note that for patients who did not use the Helpilepsy application and completed their visits remotely (via a call), questionnaires were not completed. Revised the existing footnote text stating that questionnaires **will be** administered prior to brivaracetam initiation to note that questionnaires **should be**

Number	Date	Amendment or update	Section of the protocol	Reason
				administered prior to brivaracetam initiation.
			Section 5.2 Schedule of activities, Section 8.1 Selection criteria, & Section 12.2 Planned analyses	Clarified the description of lifetime AEDs by not only excluding benzodiazepines but also any other AED used as rescue medication from the classification as a lifetime AED and adding that an AED should have been taken for at least 7 days (1 week) to be classified as a lifetime AED.
			Section 9.1 Numbering of patients	Revised text to state that patients were assigned a 5-digit number for the duration of the study instead of a 7-digit number.
			Section 10.2.4 Other safety relevant information	Added text where missing that only other relevant safety information related to brivaracetam was collected.
			Section 12.2 Planned analyses	Revised wording regarding treatment line for more clarity. Removed “name of AED” from the list of possible subgroup analyses of specific endpoints.
			Section 12.2.3.3 Analysis of other safety variables	Added a sensitivity analysis taking COVID-19 vaccine-related TEAEs into account.
			Section 12.3 Planned interim	Updated the snapshot analysis dates for the data

Number	Date	Amendment or update	Section of the protocol	Reason
			analysis and data monitoring	cutoff dates currently planned.
			Section 18.2.6 Seizure Severity Questionnaire	Updated the version of the SSQ from 3.0 to 2.1.
2	24 Oct 2022	Amendment 2.0	Section 1: Background and rationale for the study	Revised text to state that the extension of the indication in the EU for the treatment of partial-onset seizures to include patients 2 years to less than 16 years of age was approved on 24 Feb 2022.
			Section 5: Study design & Section 6: Study duration, number of patients, and sites	Updated the study design description to reflect the reduction in sample size from 600 patients to approximately 400 patients.
			Section 5.1: Visits, Section 5.2: Schedule of activities, & Section 11: Assessment of effectiveness and health-related quality of life variables	Text updated so that for patients not using the Helpilepsy application and who chose to complete their visit via a telephone call, the physician could have read the questionnaires over the phone and recorded their responses.
			Section 12.2.3.1: Analysis of other effectiveness variables	Removed text describing that machine learning techniques were to be used to model Baseline predictors of brivaracetam effectiveness in early treatment line combinations.
			Section 12.4: Determination of sample size	Added text and data supporting the sample size recalculation.

AED=antiepileptic drug; COVID-19=coronavirus 2019; PDCF=Patient Data Consent Form; SSQ=Seizure Severity Questionnaire; TEAE=treatment-emergent adverse event.

6 MILESTONES

Milestones	Planned dates	Actual dates	Comments
Protocol first approval by IEC/IRB	[redacted]		
Protocol last approval by IEC/IRB			
Amendment 1 first approval by IEC/IRB			
Amendment 2 first approval by IEC/IRB			
Start of data collection			First Patient First Visit
End of data collection			Last Patient Last Visit
Registration in the EU PAS register			
Final report of study results			

7 RATIONALE AND BACKGROUND

In the European Union, Briviact® (Nubriveo® in Italy) (brivaracetam) was initially approved, as adjunctive therapy for the treatment of POS, in patients 16 years of age and older with epilepsy on 14 Jan 2016. The extension of the indication in Europe for the treatment of POS to include patients 2 years to less than 16 years of age was approved on 24 Feb 2022. In Canada (Brivlera®), Brivaracetam was originally indicated as adjunctive therapy in the management of POS in adult (≥18 years of age) patients with epilepsy who are not satisfactorily controlled with conventional therapy. The extension of the indication in Canada for the treatment of POS to include patients ≥4 years of age was approved for the oral formulations of brivaracetam on 22 Mar 2020.

Three formulations have been developed for commercial use: film-coated tablets for oral administration (10, 25, 50, 75, and 100mg), an oral solution (10mg/mL), and a solution for intravenous injection/infusion (10mg/mL). Brivaracetam film-coated tablets, oral solution, and solution for intravenous injection/infusion show the same area under the concentration-time curve, while the maximum plasma concentration is slightly higher after intravenous administration.

Brivaracetam ([2S]-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide) is a 2-pyrrolidone derivative and displays a high and selective interaction with a brain-specific binding site, synaptic vesicle protein 2A. This binding site appears to be the major target for its pharmacological activity.

Brivaracetam is rapidly and completely absorbed throughout the gastrointestinal tract. The extent of brivaracetam absorption is not affected by food. The pharmacokinetics are dose proportional from 10mg to 600mg. Brivaracetam is weakly bound to plasma proteins (≤20%). The volume of

distribution is 0.5L/kg, a value that is close to that of total body water. The plasma half-life of brivaracetam is approximately 9 hours; the total plasma clearance in patients was estimated to be 3.6L/hour. The main metabolic pathway of brivaracetam is by hydrolysis of the acetamide group by amidase to the corresponding carboxylic acid, while a second pathway is the ω1-hydroxylation mediated by CYP2C19. The combination of these 2 pathways results in the hydroxyacid metabolite. These 3 metabolites are not pharmacologically active. There is no evidence of chiral inversion of brivaracetam. Brivaracetam is eliminated primarily by oxidative metabolism and by excretion in the urine. More than 95% of the dose, including metabolites, is excreted in urine within 72 hours after dosing; less than 10% of brivaracetam is excreted unchanged in urine.

The efficacy of brivaracetam for the adjunctive therapy of POS was established in 3 Phase 3 randomized, double-blind, placebo-controlled, fixed-dose, multicenter studies in participants 16 years of age and older. The daily dose of brivaracetam ranged from 5 to 200mg/day across these studies. All studies had an 8-week Baseline period followed by a 12-week treatment period with no up-titration. A total of 1558 patients received study drug, of which 1099 received brivaracetam. Study enrollment criteria required that patients had uncontrolled POS despite treatment with either 1 or 2 concomitant AEDs. Patients were required to have at least 8 POS events during the Baseline period. Adjunctive brivaracetam administration at doses of 50mg/day to 200mg/day without titration resulted in statistically significant and clinically relevant reductions in seizure frequency, including seizure freedom. Brivaracetam was effective and well tolerated when started at these therapeutic doses. Low incidences of AEs and low study discontinuation rates due to AEs were also observed with brivaracetam. A recent small, open-label, Phase 3 study evaluating nonpsychotic BAEs in patients receiving LEV who switched to brivaracetam showed that, at the end of the 12-week treatment period, 93.1% patients (27/29) who switched to brivaracetam had clinically meaningful reductions in BAEs, which suggests that patients experiencing BAEs associated with LEV may benefit from switching to brivaracetam (Yates et al, 2015).

The present study, EP0103, was a postmarketing, multinational, observational, prospective NIS to evaluate effectiveness, tolerability, and impact on patient quality of life of adjunctive brivaracetam therapy in earlier treatment line combinations in adult patients with history of POS.

Patients were treated according to usual medical diagnostic and therapeutic procedures; commercially available brivaracetam was prescribed according to standard clinical practice for brivaracetam. The decision to prescribe brivaracetam was separate from the decision to include the patient in the study. Other than the completion of questionnaires, no additional clinical procedures were applied to patients except at the discretion of the physician in the standard practice of medicine.

Real-time disease monitoring was assessed with an epilepsy specific electronic PRO application, Helpilepsy (on a voluntary basis). The Helpilepsy application was expected to be used by approximately half of the patients enrolled in the study with respective agreement. For those patients who did not use the Helpilepsy application, seizure information and PROs were collected via paper questionnaires and based on the medical chart information. Patient-reported questionnaires were completed voluntarily by patients. Safety reporting was completed according to all national and international regulations.

Recently published data on the postmarketing brivaracetam adjunctive experience were consistent and confirm brivaracetam to be an effective and well-tolerated therapeutic option in difficult-to-treat populations with drug-resistant epilepsy who had tried more than 3 AEDs before initiating brivaracetam (Menzler et al, 2019; Villanueva et al, 2019; Zahnert et al, 2018; Steinhoff et al, 2017; Steinig et al, 2017). The observations of these studies allow for the hypothesis that patients in earlier AED regimens might significantly benefit from combination with brivaracetam (Villanueva et al, 2019). In this NIS study, patients in earlier treatment line combinations were defined as patients who had failed no more than 3 lifetime AEDs for the treatment of seizures.

This NIS study was designed to close this existing data gap focusing on evidence for brivaracetam adjunctive therapy and on exploring possible predictions of response in earlier treatment line combinations.

8 RESEARCH QUESTION AND OBJECTIVES

The primary objective of the study was to evaluate the effectiveness of brivaracetam in earlier treatment line combinations in patients with POS with or without secondary generalization for approximately 12 months of treatment.

The secondary objective of this study was to assess the effectiveness of brivaracetam treatment in earlier treatment line combinations.

Other objectives of this study were to assess the health outcomes under brivaracetam in earlier treatment line combinations, to evaluate the speed of onset and sustained effectiveness of brivaracetam in clinical practice, to describe patient profiles for brivaracetam in earlier treatment line combinations, to assess the safety and tolerability profile (including BAEs) of brivaracetam in earlier treatment line combinations, and to assess Baseline predictors associated with brivaracetam effectiveness in earlier treatment line combinations.

9 RESEARCH METHODS

9.1 Study design

EP0103 was a postmarketing, multinational, observational, prospective NIS conducted at approximately 100 sites in Europe (Germany, Italy, Spain, and France) and Canada, with a planned 18- to 24-month Enrollment Period and an observation period of approximately 12 months per patient. Brivaracetam was prescribed according to standard clinical practice. Brivaracetam is indicated as adjunctive therapy in the treatment of POS with or without secondary generalization. Based on Protocol Amendment 2.0 (see Section 5), it was estimated that approximately 400 patients would enroll in the study (see Section 9.7).

Each patient was followed for approximately 12 months with 5 study visits as per standard clinical practice. The decision by the treating physician to prescribe brivaracetam was made before participating in the NIS. The treating physician exclusively determined the brivaracetam dose and treatment period. The study ended for each patient after the last visit within the observational period of approximately 12 months. Patients who discontinued brivaracetam treatment were withdrawn from the study. Patients could have continued brivaracetam treatment after completing the study.

Apart from requesting completion of patient-reported questionnaires (which was a voluntary decision by the patient), no additional clinical procedures were applied except as required in the standard practice of medicine. The choice of medical treatment was made independently by the treating physician in the regular course of practice and was not influenced by this NIS. For patients who refused to complete the questionnaires, the data were handled as missing information.

The study consisted of 1 cohort, and 2 interim analyses were planned and completed.

Patients had the option of completing the questionnaires and reporting seizure frequency using the Helpilepsy application for Visits 1 to 5. Helpilepsy is a digital solution electronic PRO application for real-time disease monitoring for use by patients and physicians. For those patients who did not use the Helpilepsy application, seizure information and PROs were collected via paper questionnaires and based on the medical chart information.

The schedule of activities is presented in Table 9-1.

9.2 Setting

This study was conducted in Germany, Italy, Spain, France, and Canada.

9.3 Study participants

9.3.1 Selection criteria

Before any data were collected for any patient in this NIS, written data consent was properly executed and documented.

Patients were eligible to be included in the study only if all of the following criteria applied:

1. The patient was 18 years of age or older.
2. The decision by the treating physician to prescribe brivaracetam was made independent from participation in the NIS and was in line with the drug's license and the (local) SmPC.
3. A PDCF was signed and dated by the patient.
4. The patient was considered by the treating physician to be reliable and capable of adhering to the protocol.
5. The patient had not received prior brivaracetam treatment.
6. The patient had a history of epilepsy for at least 6 months.
7. The patient had a history of partial-onset (focal) seizures. The patient must have had at least 1 POS (focal aware [simple partial], focal with impaired awareness [complex partial], or focal to bilateral tonic clonic seizure [secondarily generalized tonic clonic]) within 3 months prior to Baseline (Visit 1).
8. The patient was receiving ≥1 AED at the start of brivaracetam treatment. The patient must have failed no more than 3 lifetime AEDs used for the treatment of seizures, including all prior and concomitant AEDs at Baseline (Visit 1) before brivaracetam initiation (excluding benzodiazepines or other rescue medications used short term per physician discretion and any AED not taken for at least 7 consecutive days [1 week]).

9.3.2 Withdrawal criteria

Patients were free to withdraw from the NIS at any time, without prejudice to their continued care. Patients who had not initiated brivaracetam within 90 days of initial data consent were considered to have met withdrawal criteria. Patients who discontinued brivaracetam treatment were withdrawn from the study.

The brivaracetam treatment period was exclusively determined by the treating physician. Study participation concluded after approximately 12 months or at the time the patient withdrew his/her consent. Physicians were free to add or withdraw any medication or to withdraw the patient from the study at their own discretion.

The primary reason for withdrawal from the NIS was documented in the patient's eCRF.

The treating physician obtained information on patients in the case of withdrawal or discontinuation. For patients who discontinued the study early, the treating physician collected data as specified for Visit 5 (EOS Visit). For patients considered to be lost to follow up, the treating physician made an effort (at least 1 phone call and 1 written message to the patient) and documented his/her effort (date and summary of the phone call and copy of the written message in the source documents) to complete the final evaluation. All results of these evaluations and observations, together with the reason(s) for removing the patient, were recorded in the source documents.

9.4 Variables

The assessments of study variables are described in the following sections; the timings of the assessments are presented in the schedule of activities based on standard clinical practice (Table 9-1).

Table 9-1: Schedule of activities

	Visits				
	1[a]	2[a]	3[a]	4[a]	5[a]
Assessment	**Baseline**[b]	**3 months**[c]	**6 months**[c]	**9 months**[c]	**12 months**[c] **EOS**
PDCF signed	X				
Verification of selection criteria	X				
Demographics and other characteristics [d]	X				
General epilepsy history [e]	X				
Medical history	X				
Concomitant AEDs	X	X	X	X	X
Concomitant non-AEDs	X	X	X	X	X
Prior AED-related AEs leading to discontinuation of respective AED [f]	X				
Reason for BRV initiation	X				
BRV treatment [g]	X	X	X	X	X
Documentation of seizure information [h]	X	X	X	X	X
QOLIE-10-P [i]	X		X		X
SSQ [i]	X	X	X	X	X
NDDI-E [i]	X		X		X
CGIC		X	X	X	X
PGIC [i]		X	X	X	X
TSQM-9 [i]	X	X	X	X	X
WPAI:GH [i]	X	X	X	X	X
AEs	X	X	X	X	X
Withdrawal criteria		X	X	X	
Document completion of patient participation [j]					X

AE=adverse event; AED=antiepileptic drug; BRV=brivaracetam; CGIC=Clinical Global Impression of Change; EOS=End of Study; NDDI-E=Neurological Disorders Depression Inventory for Epilepsy; PDCF=Patient Data Consent Form; PGIC=Patient Global Impression of Change; PRO=patient-reported outcome; QOLIE-10-P=Patient-Weighted Quality of Life in Epilepsy Inventory-10-P; SSQ=Seizure Severity Questionnaire; TSQM-9=Treatment Satisfaction Questionnaire for Medication-9; WPAI:GH=Work Productivity and Activity Impairment Questionnaire: General Health.

Note: For patients who discontinued the study early, the treating physician collected data as specified for Visit 5 (EOS Visit).

[a] This visit could have been completed via a telephone call with the site.

[b] First day of brivaracetam treatment.

[c] Visits 2, 3, 4, and 5 were conducted at approximately 3, 6, 9, and 12 months, respectively, from the Baseline Visit.

[d] Demographics included: age at enrollment, sex, educational status, and employment status.

[e] Included year of first epilepsy diagnosis, lifetime AEDs (excluding benzodiazepines or other rescue medications used short term per physician discretion and any AED not taken for at least 7 days [1 week]) including reasons for discontinuation, and etiology.

[f] Collected from 6 months prior to Baseline (Visit 1).

[g] Dates and doses of brivaracetam treatment and, if discontinued, date of discontinuation and reason.

[h] The treating physician evaluated at each visit the frequency and type of seizures experienced by the patient since the prior study visit. At Baseline, seizure frequency was based on the prior 3 months to estimate the frequency per 28 days. Alternatively, seizure frequency information could have been collected via the Helpilepsy application (on a voluntary basis). Seizure frequency data may have been recorded by patients using the Helpilepsy application daily during the first week, weekly during the rest of the first month, and monthly during the rest of the study period.

[i] PRO questionnaires (QOLIE-10-P, SSQ, NDDI-E, PGIC, TSQM-9, and WPAI:GH) may have been completed within the Helpilepsy application. If a patient visiting the site was not using the Helpilepsy application, then the site staff administered paper-based questionnaires at each visit if the patient agreed to complete these questionnaires. For those patients who were not using the Helpilepsy application and who completed their visits via a telephone call, the physician read the questionnaires over the phone and recorded their responses. At Visit 1, questionnaires were answered prior to brivaracetam treatment initiation.

[j] Includes date and dose of final brivaracetam treatment in this study.

9.4.1 Primary variable

The primary variable of the study was seizure freedom for at least 6 consecutive months over a 12-month observation period.

9.4.1.1 Definition and assessment of primary variable

Patients were defined as seizure free for at least 6 consecutive months over the 12 months observation period if they met the following criterion, regardless of completion of the study:

- The patient did not report any seizures for at least 6 consecutive months over the 12 months observation period.

9.4.2 Secondary variables

The secondary variables were:

- Brivaracetam retention at 3, 6, 9, and 12 months
- Seizure freedom at 3, 6, 9, and 12 months
- POS frequency (seizures per 28 days) at Baseline, 3, 6, 9, and 12 months
- Change (absolute and percent) in POS frequency from Baseline to 3, 6, 9, and 12 months
- Response based on percent change in POS frequency at 3, 6, 9, and 12 months (response was defined as a reduction of ≥50% from Baseline)
- Discontinuation of brivaracetam due to lack of effectiveness
- Time to discontinuation of brivaracetam treatment

9.4.2.1 Definition and assessment of secondary variables

Retention was based on the number of patients remaining in the study and on brivaracetam treatment at each study visit. Patients were classed as having 3, 6, 9, and 12 months brivaracetam retention if they met the following criteria at each respective timepoint:

- The patient was still on brivaracetam within the time window of the 3, 6, 9, or 12 month visit (Table 9-2) per the study medication administration form and the duration between date of first brivaracetam administration and the visit date was at least 80, 170, 260, or 330 days, respectively. If patient had terminated the study, the duration between the date of last brivaracetam administration in the Study Termination eCRF and the date of first brivaracetam administration was at least 80, 170, 260, or 330 days, respectively.

Seizure freedom at 3, 6, 9, and 12 months was defined as no seizure reported from Baseline to 3, 6, 9, or 12 months, respectively ("No" for "Has the patient experienced any seizures since the last visit?" and 0 seizure and nonmissing data of seizure count in the Seizure Counts eCRF module at the respective visit and prior visits [as applicable]).

The treating physician evaluated at each visit, as part of standard practice with the patient, the frequency and type of seizures experienced by the patient since the prior study visit (or based on the prior 3 months at Baseline). The number of all types of POS since the last visit were reported at each visit and Month 12/EOS Visit. The 28-day seizure frequency for all types of POS was calculated as:

$$\frac{\text{Number of all types POS recorded since previous visit}}{\text{(Date of current visit – Date of previous visit + 1)}} \times 28$$

All types of POS frequency were only calculated at visits recorded and with seizure data recorded. For seizure frequency summaries, data recorded at the EOS Visit for the study earlier than the 12 months visit were mapped to the appropriate scheduled visits (see Section 9.9.2) and visit date was obtained from the eCRF visit date page.

Twenty-eight-day Baseline all types POS frequency (28-day Baseline) was calculated using the Historical Seizure Count eCRF page, as the number of all types POS recorded during the 3 months prior to first brivaracetam administration/3.

The following variables were defined for each visit and Month 12/EOS Visit using the 28-day Baseline and 28-day post-Baseline seizure frequency variables described below.

- Absolute reduction in all types of POS frequency defined as:
  28-day Baseline – 28-day post-Baseline seizure frequency
- Percentage reduction in all types of POS frequency defined as:
  $$\frac{\text{28-day Baseline seizure frequency – 28-day post-Baseline seizure frequency}}{\text{28-day Baseline}} \times 100$$
  Patients without all types of POS at Baseline were not included in the percent reduction calculation for summary.
- Patients without any POS at Baseline were excluded from the analysis of percentage reduction and response (≥50%).

- Response (Yes, No) where Yes was ≥50% reduction in all types of POS frequency calculated as described above and No otherwise.

Discontinuation of brivaracetam due to lack of effectiveness (captured on the eCRF as "lack of efficacy") was collected from the Study Medication Discontinuation eCRF.

A patient was considered to have a discontinuation event only if the patient discontinued brivaracetam or the Study Termination eCRF page was completed with patient status at study termination of Dropout. Patients who completed the study (patient status at study termination of Completed) were considered to not have had an event and were censored. The censored date was the date of last brivaracetam administration date in the Study Termination eCRF or the date of study termination, whichever came first.

Time to discontinuation of brivaracetam (days) was calculated as:

Date of last administration of brivaracetam while in the study (Study Termination eCRF page) – date of first brivaracetam administration (First Dose of Medication Received During Reference Period eCRF page) + 1.

9.4.3 Other variables

9.4.3.1 Other effectiveness variables

The other effectiveness variables were:

- Self-reported seizure frequency collected at each available timepoint (daily during the first week, weekly during the rest of the first month, and monthly during the rest of the study period)
- Time to first seizure after first dose of brivaracetam

9.4.3.1.1 Definition and assessment of other effectiveness variables

Analysis of self-reported seizure frequency by types of seizure (number of all seizures, generalized seizures, partial seizures evolving to secondary generalized, POS) and the time to first seizure after first dose of brivaracetam were based on the data collected from the Helpilepsy application. The use of the Helpilepsy application within the study is described in Section 9.5.

The time to the first seizure (days) was calculated as:

Date of first seizure in the study – date of first brivaracetam administration + 1

9.4.3.2 Other health outcome variables

The other health outcome variables were:

- PGIC rating at 3, 6, 9, and 12 months
- CGIC rating at 3, 6, 9, and 12 months
- QOLIE-10-P total score at Baseline, 6, and 12 months
- Change in QOLIE-10-P total score from Baseline to 6 and 12 months
- TSQM-9 scores at Baseline, 3, 6, 9, and 12 months
- Change in TSQM-9 scores from Baseline to 3, 6, 9, and 12 months

- WPAI:GH scores at Baseline, 3, 6, 9, and 12 months
- Change in WPAI:GH scores from Baseline to 3, 6, 9, and 12 months
- NDDI-E total score at Baseline, 6, and 12 months
- Change in NDDI-E total score from Baseline to 6 and 12 months
- SSQ rating for questions 5 (yes/no responses) and 8 at Baseline, 3, 6, 9, and 12 months

9.4.3.2.1 Definition and assessment of health outcome variables

The analysis of health outcome data was done based on data from both paper questionnaires and the Helpilepsy application.

The QOLIE-10-P version 2 was used to evaluate the health-related QoL of study patients (Cramer and Van Hammée, 2003; Cramer et al, 1996). The QOLIE-10-P is an adaptation of the original QOLIE-31 instrument (Cramer et al, 1998). The QOLIE-10-P is a brief survey completed by the patient assessing health-related quality of life of adults with epilepsy. There are 10 questions about health and daily activities, 1 question about the level of epilepsy-related quality of life distress, and a ranking of importance for each of the 7 concepts assessed with the questionnaire. The QOLIE-10-P total score ranges from 0 to 100 with higher scores reflecting better functioning. The epilepsy distress score ranges from 10 to 100 with higher score reflecting lower levels of distress.

The Clinical Global Impression scales (Guy and Bonato, 1970) were initially developed for a risk-benefit evaluation within the treatment of mentally ill patients. The 4 global scales (Severity of Illness, Change in Severity from Baseline, Therapeutic Efficacy, and Tolerability of Treatment) are used as different measures of treatment outcome in different kinds of pharmacological studies. The scale on change in severity from Baseline used in this study asked the clinician to rate the patient's condition over the past 4 weeks compared with Baseline, and response options range from 1 (very much improved) to 7 (very much worse).

Similarly to the CGIC, the PGIC (Hurst and Bolton, 2004) is a 7-point categorical rating scale in which the patients are asked to rate how they have felt over the past 4 weeks compared with before they entered the study. Response options range from 1 (very much improved) to 7 (very much worse). The PGIC was completed during an interview between the patient and the treating physician or designee.

The TSQM is a general tool for assessing a patient's satisfaction with medications designed to treat, control, or prevent a wide variety of conditions. It includes 14 items and 4 domains: Effectiveness (Questions 1 to 3), Side Effects (Questions 4 to 8), Convenience (Questions 9 to 11), and Global Satisfaction (Questions 12 to 14). In this study, an abbreviated 9-item TSQM (TSQM-9) (Bharmal et al, 2009) without the side effects subscale was used. For each of the 3 domains assessed, a score was generated ranging from 0 to 100 with higher scores reflecting higher effectiveness, convenience or satisfaction.

The WPAI:GH (Reilly et al, 1993) consists of 6 items allowing to generate 4 scores measuring absenteeism, presenteeism (the percentage of impairment experienced while at work), overall work productivity loss, and activity impairment. Only employed respondents provided data for the work-related items, but all respondents provided data for activity impairment. Each of the

4 scores range between 0 and 100 with higher scores reflecting higher work or activity impairment.

The SSQ (Cramer et al, 2002) is a facilitated interview during which a clinician reviews seizure attributes with the patient and an observer (someone who regularly observes the seizures). In this study, a modified version of the SSQ was used that was comprised only of question 5 assessing the presence of cognitive effects after seizures with 3 subquestions assessing the frequency, intensity, and bothersomeness of these cognitive effects; and question 8 assessing the overall severity of the seizures experienced by the patient over the past 4 weeks.

The NDDI-E (Gilliam et al, 2006) is a 6-item questionnaire developed to screen for depression in people with epilepsy. The NDDI-E was completed by the patients. The NDDI-E score ranges from 6 to 24, with higher scores reflecting more severe depressive symptoms. A cutoff of >15 was proposed to screen possible major depressive disorders (Friedman et al, 2009).

9.4.3.3 Safety variables

The safety variables were:

- Incidence of TEAEs
- Incidence of behavioral TEAEs
- Incidence of serious TEAEs
- Incidence of serious behavioral TEAEs
- Incidence of study drug-related TEAEs
- Incidence of study drug-related, behavioral TEAEs
- Incidence of TEAEs leading to brivaracetam discontinuation
- Incidence of behavioral TEAEs leading to brivaracetam discontinuation
- Incidence of AESI
- Incidence of OSR information
- Incidence of prior AED-related AEs leading to discontinuation of respective AED
- Discontinuation of brivaracetam due to a TEAE
- Exposure to brivaracetam

9.4.3.3.1 Definition and assessment of safety variables

An AE was any untoward medical occurrence in a patient or clinical investigation patient administered a medicinal product that did not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

A TEAE was defined as an AE which had an onset on or after the date of first brivaracetam administration up to 4 weeks (28 days) after brivaracetam discontinuation.

An AE was serious if 1 or more of the following criteria were met:

- Death
- Life threatening: An event in which the patient was at risk of death at the time of the event. It did not refer to an event which hypothetically might have caused death if it were more severe.
- Inpatient hospitalization or prolongation of existing hospitalization: If a hospitalization was planned prior to the patient receiving the first dose of medicinal product, it was not classified as serious. However, if a hospitalization was unplanned and was a result of an adverse experience, this was considered an SAE.
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- An important medical event or an event requiring significant intervention: Medical and scientific judgment was exercised in other situations, such as important medical events that may not have been immediately life threatening or resulted in death or hospitalization but may have jeopardized the patient or may have required intervention to prevent one of the other outcomes listed in the above definition. These were usually considered serious.

Behavioral TEAEs are a list of PTs selected from MedDRA and are presented in a separate TEAE table. The list of PTs can be found in Section 6.4 of the SAP.

An AESI was any AE that a regulatory authority mandated to be reported on an expedited basis, regardless of seriousness, expectedness, or relatedness of the AE to the administration of a UCB product. The following were AESIs for this study:

- Autoimmune nephritis
- Nephritis
- Nephritis allergic
- Tubulointerstitial nephritis
- Tubulointerstitial nephritis and uveitis syndrome
- Drug induced liver injury

Other safety relevant information included the following:

- Off-label use of brivaracetam: Situation where brivaracetam was intentionally used for a medical purpose not in accordance with the authorized product information
- Misuse of brivaracetam: Situation where brivaracetam was intentionally and inappropriately used not in accordance with the authorized product information
- Abuse of brivaracetam: Persistent or sporadic, intentional excessive use of brivaracetam, which was accompanied by harmful physical or psychological effects
- Medication error of brivaracetam: Any unintentional error in the prescribing, dispensing, or administration of brivaracetam while in the control of the healthcare professional or patient

- Occupational exposure of brivaracetam: Exposure to brivaracetam (as defined in 2010/84/EU Article 1) as a result of one's professional or nonprofessional occupation
- Lack of therapeutic effectiveness of brivaracetam
- Overdose of brivaracetam
- Suspected transmission of an infectious agent via brivaracetam
- Suspected adverse reaction associated with a suspected or confirmed falsified medicinal product or quality defect (combined complaint) of brivaracetam
- Unexpected therapeutic effect of brivaracetam

The patient was considered to be having a prior AED-related AE leading to discontinuation of respective AED if the following criteria were met:

- Side effect was ticked for primary reason for discontinuation from the History of Previous AED eCRF page. If "side effects" was ticked the patient had an AE leading to discontinuation of that AED
- AED had a stop date within the time period of 6 months prior to Baseline (Visit 1)

The main reason for brivaracetam discontinuation due to TEAE was recorded in the Study Medication Discontinuation eCRF page, with the main reason for brivaracetam discontinuation "behavioral side effects" or "other intolerance".

The duration of exposure to brivaracetam while in the study was calculated as:

> Duration of exposure to brivaracetam (days) = Date of last administration of brivaracetam while in the study – date of first brivaracetam administration + 1.

For listing purposes, as each brivaracetam administration was recorded as 1 observation in the brivaracetam administration log, the duration of brivaracetam administration (days) was considered and calculated as below:

> Duration of brivaracetam administration (days) as records = End date of administration of brivaracetam as record – Start date of first brivaracetam administration as record + 1.

9.5 Data sources and measurement

Effectiveness, tolerability, and quality of life data were collected from patients who were prescribed adjunctive brivaracetam as per local label. These data were collected from patients as they completed site or telephone visits according to the schedule of study assessments based on standard clinical practice.

The choice of medical treatment was made independently by the treating physician in the course of regular practice and was not influenced by the study.

Within this NIS, the Helpilepsy application was offered as an option to the participating sites and patients. The use of the Helpilepsy application within the study was voluntary and limited to data collection on seizure frequency and patient-reported questionnaires (automatically sent to patients to be completed on a voluntary basis). For those patients who did not use the Helpilepsy application, PROs could have been recorded via paper questionnaires and based on the medical chart information. Alternatively, if the patient agreed to complete the questionnaires over the

phone, the physician read the questions directly and recorded the patient's responses. The treating physician evaluated at each visit, as part of standard practice with the patient, the frequency and type of seizures experienced by the patient since the prior study visit (or during the prior 3 months at Baseline).

Data collected from Helpilepsy were used for analysis of time to first seizure after first dose of brivaracetam as well as change over time in other health outcomes: SSQ, QOLIE-10-P, TSQM-9, NDDI-E, WPAI:GH, PGIC, and CGIC.

9.6 Bias

All NIS are subject to different types of bias. In this study, the following types of bias were identified:

- Recall bias: PROs were recorded either electronically via the Helpilepsy application by the patient or, using paper questionnaires, completed by the patient or the treating physician based on patient self-assessments.
- Selection bias:
  - Site selection bias: This bias arises when patient recruitment is limited to known high-quality or specialized facilities, implying that patients could receive a higher level of care, reflected in better outcomes. In EP0103 NIS, site selection varied between countries and within countries, with not all sites being epilepsy centers (ie, EP0103 enrolled patients from specialized and nonspecialized facilities [eg, general neurologists]); thus, minimizing the site selection bias.
  - Patient selection bias: There is a potential source of patient selection bias present in any study where investigators identify eligible patients based on specific selection criteria. In EP0103 NIS, selection criteria were less restrictive than in an interventional study to ensure the study population is representative of the real-world patient population; thus, minimizing the impact of patient selection bias on the study outcomes.
  - Nonresponse bias: This type of bias applies to enrolled patients who discontinue the study and to patients who remain in the study but do not respond to all assessments. This type of bias matters as nonresponders are expected to be systematically different from patients who complete all assessments. For example, these patients might be different in terms of age, disease duration or severity, comorbidities, etc., and therefore, their outcomes might differ compared with the patients included in the analyses. However, to address a nonresponse bias, EP0103 had a large sample size and a wide selection of patients due to less restrictive selection criteria included in the analyses.

9.7 Study size

Taking into consideration some drop out during the study period, originally a sample of 600 eligible patients was planned for the study to result in 500 patients being included in the SS.

Due to unforeseen delays in enrollment, including the COVID-19 pandemic, the sample size was reduced from 600 patients to 400 patients in Protocol Amendment 2.0. Assuming a discontinuation rate of 15%, a sample size of 400 patients would yield 340 evaluable patients. For the expected seizure freedom rate of 50%, the 2-sided 95% CI for a single proportion using

large sample normal approximation would extend by 5.3% from the observed proportion corresponding to a CI of 44.7% to 55.3%.

A more conservative scenario considered 380 enrolled patients prior to the end of enrollment, with 320 patients remaining after premature discontinuations. In this scenario, the 2-sided 95% CI for a single proportion using large sample normal approximation would extend 5.5% from the observed proportion if the expected proportion was 50%. This corresponds to a CI of 44.5% to 55.5%. As such, reduction of the sample size still preserved the primary objective and scientifically meaningful outcome of the study.

9.8 Data transformation

Data handling is described in detail in Section 9.10.2.

Helpilepsy data, including electronic PROs, were loaded into the database per standard procedures documented in the Integration Test Script. Paper PROs were entered into the database by the sites.

9.9 Statistical methods

9.9.1 Populations for analysis

- The APD was defined as all patients included in the study with valid data consent and for whom at least Visit 1 (Baseline) was documented. The APD was used for patient disposition and patient data listings only.
  - "Valid data consent" was defined as the patient having a valid date present for signature of the PDCF.
  - A patient had completed Visit 1 (Baseline) if a valid visit date for Baseline was present. If this Visit 1 (Baseline) date was missing, a date of any assessment at Baseline may also have represented a completed Baseline visit.
- The SS was defined as all patients included in the APD that received treatment with brivaracetam at least once in the study, according to the following criteria. The SS was used for the analysis of all study variables.

  A patient was considered to have received at least 1 brivaracetam treatment if at least 1 date of brivaracetam administration (any date on Study Medication Administration eCRF or "Date of first administration of brivaracetam during the study" on the First Dose of Medication Received During Reference Period eCRF or "Date of last administration of brivaracetam while in the study" on the Study Termination eCRF) was present on or after the Baseline Visit date; OR at least 1 brivaracetam dose was present in the database from Study Medication Administration eCRF.
- The PPS was defined as all patients in the SS who were treated according to the approved SmPC during their observation period, representing the on-label use of brivaracetam in Europe and Canada. Any patient with a documented protocol deviation may have been excluded from the PPS. The PPS was used for the analysis of all study variables.

  Compliance with approved SmPC was defined as follows if the patient was considered to have been treated according to the approved SmPC:

- Patient had POS with or without secondary generalization at Baseline as recorded in the Historical Seizure Count eCRF page at Baseline, with complete and valid data for field "all types of partial-onset seizures experienced" or "partial-onset seizures with secondary generalization experienced".
- All documented brivaracetam doses were both less than or equal to the maximum approved dose of 200mg/day and greater than or equal to the minimum approved dose of 50mg/day (with the exception of down-titrating). Per the SmPC, a down titration of brivaracetam was allowed to 20mg/day; hence, any patients who received brivaracetam doses lower than 50mg/day from Day 2 onwards were reviewed during the DEM to determine whether they were taking brivaracetam per SmPC.
- Brivaracetam was administered as an adjunctive therapy, defined as:
  Patient was receiving at least 1 concomitant AED at Baseline and during the treatment period with brivaracetam as recorded in Concomitant AED Medicine eCRF page, with valid data for any of the following fields for each medication: medication name, start or stop date/ongoing. The comprehensive review of concomitant AED was performed during the DEM.

9.9.2 Main summary measures

General study level definitions can be found in Section 5.1.1 of the SAP.

All variables were summarized using descriptive statistics; there were no inferential analyses. For continuous variables, summary statistics (number of available observations, mean, standard deviation, minimum, median, maximum, the 25% and 75% quartiles and interquartile range where relevant) were tabulated. In general, the mean, median, quartiles, and standard deviation were displayed to 1 more decimal place than collected in the source data. Minimum, maximum, and range were displayed to the same number of decimals used for the source data.

Categorical variables were summarized by the number and percentage in each category. If there were no patients in a specific category, that row was retained and 0 presented in the table. For tables such as demographics and Baseline characteristics, if there were patients with missing data for a categorical variable, a missing row was added, and percentages were based on the number of patients in the analysis set (N). For visit-based analysis, including PRO questionnaire and effectiveness endpoints (except brivaracetam retention), percentages were based on the denominator for number of patients who completed the respective timepoint with nonmissing data. For other nonvisit-based analysis, including demographic, Baseline characteristics, prior and concomitant medication, exposure, AEs, other safety related analysis, and brivaracetam retention percentages were based on the number of patients in the analysis set (N).

Unless otherwise noted, all percentages were displayed to 1 decimal place. No percentage was displayed for zero counts, and no decimal was presented when the percentage displayed was 100%.

For patients who discontinued prior to Month 12, the last visit within the study and respective assessments were mapped to the relevant visit per the schedule of activities based on the following table by using the days of last visit from Baseline (relative day is defined in Section 5.1.1.1.1 of the SAP):

Table 9-2: Mapping windows

Variables	Visit 2, Month 3 (Relative day)	Visit 3, Month 6 (Relative day)	Visit 4, Month 9 (Relative day)	Visit 5, Month 12 (Relative day)
BRV administration	2-135	136-225	226-315	≥316
Seizure freedom	45-135	136-225	226-315	≥316
Seizure frequency	45-135	136-225	226-315	≥316
CGIC	45-135	136-225	226-315	≥316
PGIC	45-135	136-225	226-315	≥316
QOLIE-10-P	No mapping	120-270	No mapping	≥271
TSQM-9	75-135	136-225	226-315	≥316
WPAI:GH	45-135	136-225	226-315	≥316
NDDI-E	No mapping	90-270	No mapping	≥271
SSQ	75-135	136-225	226-315	≥316

BRV=brivaracetam; CGIC=Clinical Global Impression of Change; NDDI-E=Neurological Disorders Depression Inventory for Epilepsy; PGIC-Patient Global Impression of Change; QOLIE-10-P=Patient-Weighted Quality of Life in Epilepsy Inventory-10-P; SSQ=Seizure Severity Questionnaire; TSQM-9=Treatment Satisfaction Questionnaire for Medication-9; WPAI:GH=Work Productivity and Activity Impairment Questionnaire: General Health.

In addition to the premature study termination visit, the Helpilepsy application, where used, collected completion dates for health outcome questionnaires and the corresponding Visit was also mapped as above.

Assessments at premature study termination visit were summarized at the appropriate visit corresponding to the date of the assessment in the mapping table.

9.9.2.1 Subgroup analyses

Subgroup analysis was performed with the following subgroup categories:

- Number of lifetime AEDs (eg, subgroup categories 0, 1, 2, 3, and >3)
- Number of concomitant AEDs (eg, subgroup categories 1, 2, 3, and >3)
- Treatment line in adjunctive therapy (eg, subgroup categories of brivaracetam as adjunctive therapy; first, second, third or later adjunctive treatment)
- 28-day Baseline all types of POS frequency (eg, subgroup categories of 0, >0 to <1, 1 to 5, >5 to 10, >10)

Subgroup analyses of specific endpoints (seizure freedom for at least 6 consecutive months; seizure freedom at 3, 6, 9, and 12 months; brivaracetam retention at 3, 6, 9, and 12 months) were performed on the SS and the PPS, including number of lifetime AEDs, number of concomitant AEDs, treatment line in adjunctive therapy (ie, brivaracetam added as first, second, third, or later adjunctive treatment), and Baseline all seizure frequency.

The treatment line in adjunctive therapy was defined as below:

- Brivaracetam added as first adjunctive treatment line: at least 1 AED ongoing (at brivaracetam first dose); no adjunctive therapy before brivaracetam first dose
  - Possible overlapping of AEDs for ≤2 month was allowed and not considered to be adjunctive treatment (= due to possible titration period)
- Brivaracetam added as second adjunctive treatment line: at least 1 AED ongoing (at brivaracetam first dose); max 1 adjunctive therapy before first brivaracetam dose
  - Possible overlapping of AEDs for ≤2 month was allowed and not considered to be adjunctive treatment (= due to possible titration period)
- Brivaracetam added as third adjunctive treatment line: at least 1 AED ongoing (at brivaracetam first dose); max 2 adjunctive treatment before first dose of brivaracetam
  - Possible overlapping of AEDs for ≤2 month was allowed and not considered to be adjunctive treatment (= due to possible titration period)
- Later adjunctive treatment line: any patient not meeting the criteria of first, second, or third adjunctive treatment line definition
  - Possible overlapping of AEDs for ≤2 month was allowed and not considered to be adjunctive treatment (= due to possible titration period)

9.9.3 Main statistical methods

All analyses were performed using SAS® (Statistical Analysis System) version 9.3 or higher (SAS Institute, Cary, NC, USA). AEs and medical history were coded using version 18.1 of MedDRA. Medications were coded using the Sep 2020 B3 update version of WHODD.

Data from patients who prematurely withdrew from the study were analyzed up to the final visit attended.

Outputs displayed results by the patient population as well as columns indicating the patient's country in patient listings.

Baseline visit data were defined as the data collected at Visit 1. For concomitant and prior medications and AEDs, Baseline was defined with respect to the date of first brivaracetam administration. Prior medication (history of previous AED treatment) was collected up to 6 months prior to Baseline. Baseline seizure frequency was based on the 3 months prior to Visit 1 (Baseline) to estimate the frequency per 28 days. For the patient questionnaires collected via Helpilepsy application or paper, Baseline (Visit 1) was defined as data collected up to 7 days after first brivaracetam administration (Questionnaire completed date – first brivaracetam administration + 1≤7 days).

Two informal interim analyses (snapshot analyses) were performed. These were descriptive analyses. Data from the interim analysis were prepared and reviewed by UCB and the designated CRO (Parexel).

9.9.3.1 Primary outcome variables

The primary analysis was summarized as the number and percentage of patients with seizure freedom for at least 6 consecutive months by visit within the total observation period of 12 months for the SS and repeated for the PPS.

A 2-sided 95% CI for the seizure freedom rate was also presented and was estimated using exact binomial CI (Clopper-Pearson method).

The seizure freedom rate was defined as the percentage of patients who achieved seizure freedom for at least 6 consecutive months at any point over the approximately 12 months of observation. To calculate the percentage, the denominator was the number of patients who completed the respective timepoints with nonmissing data.

In addition to the summary of overall number and seizure freedom rate for 6 consecutive months, the below timeframe of seizure freedom rate was also shown:

- The number and seizure freedom rate at Baseline onwards to Visit 3 (Month 6) for 6 months
- The number and seizure freedom rate at Visit 2 (Month 3) onwards to Visit 4 (Month 9) for 6 months
- The number and seizure freedom rate at Visit 3 (Month 6) onwards to Visit 5 (Month 12) for 6 months

In addition, a by-patient listing of seizure freedom was produced on the SS including seizure freedom at 3, 6, 9 and 12 months (yes/no for "Has the patient experienced any seizure since last visit?") and the days between visits, which were listed together within the same listings of time to the first seizure.

9.9.3.2 Secondary outcome variables

9.9.3.2.1 Brivaracetam retention at 3, 6, 9, and 12 months

Number of patients and brivaracetam retention rates at 3, 6, 9, and 12 months were summarized for the SS and repeated for the PPS. Percentages were based on the number of patients in the analysis set (N), or nonmissing frequency (n) by timepoint (where applicable).

In addition, subgroup analyses (described in Section 9.9.2.1) were performed for both the SS and the PPS. A 2-sided 95% CI for the brivaracetam retention rate was presented and estimated by using exact binomial CI (Clopper-Pearson).

A by-patient listing of brivaracetam retention including dates of first and last brivaracetam administration, brivaracetam study medication discontinuation, and derived brivaracetam retention flag (Yes, No) at 3, 6, 9, and 12 months was provided for the SS.

9.9.3.2.2 Seizure freedom at 3, 6, 9, and 12 months

The analyses were performed using similar methodology as for the primary variable. Number of patients and seizure freedom rate at 3, 6, 9, and 12 months were summarized for the SS and repeated for the PPS. In addition, subgroup analyses (described in Section 9.9.2.1) were performed for both the SS and the PPS.

A 2-sided exact (Clopper-Pearson) 95% CI for the seizure freedom rate was also presented. Percentages were based on the denominator of number of patients who completed the respective timepoint with nonmissing data.

9.9.3.2.3 Seizure frequency

Descriptive statistics of the POS frequency (seizures per 28 days), absolute reduction in POS frequency, and percent reduction in POS frequency at 3, 6, 9, and 12 months were presented for

the SS and repeated for the PPS. Number of patients and responder rate (≥50% reduction in POS frequency from Baseline) at 3, 6, 9, and 12 months were summarized for the SS and for the PPS.

Seizure data were also presented in listing format and included the following:

- Seizure frequency by type (including by visit date of number of all seizures, POS, POS with secondary generalized seizures, and generalized onset seizures) at Baseline, since the last visit, and adjusted for 28-day frequency. In addition, the number of days since last visit, and the 28-day adjusted POS frequency absolute and percentage reduction from Baseline were presented.

9.9.3.2.4 Discontinuation of brivaracetam due to lack of effectiveness

Number and percentage of patients with discontinuation of brivaracetam due to lack of effectiveness were summarized for the SS and repeated for the PPS.

9.9.3.2.5 Time to discontinuation of brivaracetam treatment

A Kaplan-Meier analysis of time to discontinuation of brivaracetam was provided on the SS and repeated for the PPS. The median time to event (days) was presented along with the 25% and 75% quartiles and 95% CIs.

9.9.3.3 Other variables

9.9.3.3.1 Other effectiveness variables

Data collected via Helpilepsy

Self-reported seizure frequency by type of seizure (number of all seizures, generalized seizures, partial evolve to secondary generalized, POS) collected via Helpilepsy for all types of seizure were summarized by timepoint as defined below for the SS and repeated for the PPS:

- Daily seizure count during the first week (from first brivaracetam administration day to Day 7 of brivaracetam administration)
- Weekly seizure count from Week 2 to Week 4 after first brivaracetam administration
- Monthly seizure count from Month 2 to Month 12/EOS Visit (30-day window)

The time to first seizure after first dose of brivaracetam was analyzed based on seizure data collected from Helpilepsy application as data collected in this application contained sufficient details for this calculation. The dates of seizures were recorded and loaded via electronic data transfer.

The time to first seizure from the date of first dose of brivaracetam was analyzed using Kaplan-Meier methods, from which the median time to first seizure was calculated along with quartiles and their respective 95% CIs. In addition, the cumulative number of events, number at risk, and survival estimate at monthly intervals was provided. The survival curve was displayed for the Kaplan-Meier analysis. This was performed on the SS and repeated for the PPS.

9.9.3.3.2 Health outcome variables

Analyses of all health outcome variables listed below were performed on the SS and the PPS. The analysis of PRO data was conducted on data from paper questionnaires and the Helpilepsy application.

For the CGIC and the PGIC, the number and percentage of patients improved (sum of minimally, much, and very much), remained unchanged and worsened (sum of minimally, much and very much) and in each individual categories of improvement and worsening were described at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12). Histograms with each CGIC and PGIC rating and how many patients had improved, had no change, or worsened were produced for the SS and the PPS.

Descriptive statistics were produced for the QOLIE-10-P total score at Visit 1 (Baseline), Visit 3 (Month 6) and Visit 5 (Month 12) as well as changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 5 (Month 12), respectively. The line plot for mean change from Baseline in QOLIE-10-P total score was produced by visit for the SS and the PPS.

In addition, descriptive statistics were produced for the QOLIE-10-P epilepsy distress score (Question 11) and each domain ranking (Question 12) at Visit 1 (Baseline), Visit 3 (Month 6) and Visit 5 (Month 12) as well as changes from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 5 (Month 12), respectively. Line plots for mean change from Baseline in QOLIE-10-P epilepsy distress score and each domain ranking were produced by visit for the SS and PPS.

Descriptive statistics were produced for the TSQM-9 domain scores (Effectiveness, Convenience and Global Satisfaction) at each visit, and for the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12), respectively. A line plot for mean change from Baseline in TSQM-9 domain scores (Effectiveness, Convenience and Global Satisfaction) presented by visit was produced for the SS and the PPS.

Descriptive statistics were produced for the 4 WPAI:GH dimensions scores (percent time work missed due to health problem, percent impairment while working due to health problem, percent overall work impairment due to health problem, percent activity impairment due to health problem) at each visit, and the changes from Visit 1 (Baseline) to Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12), respectively.

Descriptive statistics were produced for the NDDI-E score at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 5 (Month 12) and change in score from Visit 1 (Baseline) to Visit 3 (Month 6) and Visit 5 (Month 12), respectively.

The number and percentage of patients responding yes/no to question 5 (the presence of cognitive effects after seizures) were described; and for patients with a positive response, descriptive statistics were produced for the 3 subquestions. Descriptive statistics were also produced for question 8 (severity of seizures in the past 4 weeks). In addition, a shift table for SSQ question 5 responses (yes/no) of each post-Baseline visit versus Baseline was summarized for the SS and the PPS.

The scoring rules of the QOLIE-10-P, CGIC, PGIC, TSQM-9, WPAI:GH, SSQ and NDDI-E are described in Section 5.5.1.1.3 of the SAP.

9.9.3.3.3 Safety variables

All exposure analyses were performed on the SS and repeated for PPS.

If dates were missing or multiple dates were available, the last administration of brivaracetam date was considered in the following order of priority: date of first brivaracetam administration date, last contact date, and date of last visit date.

For assigning dose records to a specific visit, if the patient had multiple brivaracetam records at the same visit, the dose adjustment of this patient only considered the dosing records at or closest to the scheduled visit date. The visit mapping of brivaracetam administration was used (see Table 9-2) by considering the relative day for brivaracetam administration start date and end date. If a total daily dose for a patient was across multiple visits, then this dose appeared as the total daily dose for each visit.

In addition, the following categories of duration of exposure (days) display the number of patients as below for the SS and repeated for the PPS:

- 1 day to <3 months brivaracetam (1-<90 days)
- 3 months to <6 months brivaracetam (90-<180 days)
- 6 months to <9 months brivaracetam (180-<270 days)
- 9 months to <12 months brivaracetam (270-<360 days)
- ≥12 months brivaracetam (≥360 days)

The number and percentage of patients receiving each daily brivaracetam dose at Baseline (Visit 1), Visit 2, Visit 3, Visit 4, and Visit 5 were summarized in the following brivaracetam dosing categories.

- ≤10mg
- >10 to <50mg
- ≥50mg to <100mg
- ≥100mg to <150mg
- ≥150mg to ≤200mg
- >200mg

By-patient listing of exposure to brivaracetam while on study (including the start and end dates of brivaracetam, duration of brivaracetam administration [days] records, and total daily dose) were provided on the SS.

All AEs and OSR information occurring during the study (ie, on or after signing the PDCF) were required to be reported. Analyses focused on TEAEs; however, a listing of all AEs recorded in the database was also provided.

AEs were summarized by MedDRA SOC and PT for the SS. The following summaries, including the number of events and the number and percentage of patients who experienced the event, were provided for the SS and were also repeated on the PPS:

- Overview of TEAEs (including categories for any TEAE, serious TEAEs, patient discontinuations due to TEAEs [derived as “Action Taken with Study Medication = Drug permanently withdrawn”], brivaracetam drug-related TEAEs, all deaths [AEs leading to death])
- Incidence of TEAEs
- Incidence of TEAEs above reporting threshold of 5%

- Incidence of behavioral TEAEs
- Incidence of serious TEAEs
- Incidence of serious behavioral TEAEs
- Incidence of TEAEs reported by the investigator as brivaracetam drug-related
  - Derived as related to study medication = “Yes”
- Incidence of TEAEs reported by the investigator as brivaracetam drug-related or missing
  - Derived as related to study medication = “Yes” or “Missing”
- Incidence of brivaracetam drug-related behavioral TEAEs
  - Derived as behavioral TEAEs related to study medication = “Yes”
- Incidence of TEAEs leading to brivaracetam discontinuation
  - Derived as action taken with study medication = “Drug permanently withdrawn”
- Incidence of behavioral TEAEs leading to brivaracetam discontinuation
  - Derived as action taken with study medication = “Drug permanently withdrawn”
- Incidence of AESI
- Incidence of OSR events
- Incidence of prior AED-related AEs leading to discontinuation of respective AED
  - The patient was considered to have prior AED-related AEs leading to discontinuation of respective AED if the following criteria were met:
  - Side effect was ticked for primary reason for discontinuation on the History of Previous AED eCRF page. If "side effects" was ticked the patient had an AE leading to discontinuation of that AED.
  - AED had a stop date within the time period collected from 6 months prior to Baseline (Visit 1).
- Discontinuation of brivaracetam due to a TEAE
  - The number and percentage of patients with main reason for brivaracetam discontinuation due to TEAE (as recorded in the Study Medication Discontinuation eCRF page, with the main reason for brivaracetam discontinuation "behavioral side effects" or "other intolerance")

In addition, the following by-patient listings for the APD were presented including the MedDRA SOC and PT, reported term, onset and outcome date, duration, seriousness, intensity, pattern, belonging to TEAE or AESI, outcome, relationship to study medication, and action taken with regards to study medication:

- All AEs
- All SAEs

- All AEs leading to permanent discontinuation of brivaracetam
- All deaths (AEs leading to death)

Due to the COVID-19 pandemic occurring at the time of the initiation of this study, COVID-19-related TEAEs were explored and displayed separately. An analysis was performed of COVID-19-vaccine-related TEAEs as well as total TEAEs excluding COVID-19-vaccine-related TEAEs (derived as "Is the Event related to a Covid-19 Vaccination? = Y" from the Adverse Event eCRF page). The COVID-19-related data were incorporated into the tabulations of medical history and AEs. In addition, patients who received 1 or more doses during the study (if applicable) of a COVID-19 vaccine (captured in the Concomitant Medications eCRF page) were presented with respect to TEAEs.

9.9.4 Missing data

For patients who completed or withdrew from the study, if the date of last brivaracetam administration was missing, then the last end date from the brivaracetam administration in the Study Medication eCRF page (applying the imputation of partial end dates rules, as required) was used. The date of last contact was used for the calculations if the last brivaracetam administration date was missing; otherwise, the date of last visit was applied if the date of last contact was not available.

Partial dates may have been imputed for statistical analyses for specific outcomes according to the following rules. In general, imputed dates were not shown in listings with the exception of showing imputed dates alongside partial dates for key derivations.

Partial dates may have been imputed for the following reasons:

- Classification of AEs as TEAEs
- Classification of medications as prior or concomitant (AED and non-AED medication)
- Durations of AE

Imputation of partial start dates for AE and prior/concomitant medication:

- If only the month and year were specified and the month and year of first dose was not the same as the month and year of the start date, then the first of the month was used.
- If only the month and year were specified and the month and year of first dose was the same as the month and year of the start date, then the date of first brivaracetam administration was used.
- If only the year was specified, and the year of first dose was not the same as the year of the start date, then 01 Jan of the year of the start date was used.
- If only the year was specified, and the year of first dose was the same as the year of the start date, then the date of first brivaracetam administration was used.
- If the start date was completely unknown, then the date of first brivaracetam administration was used. Manual review may have been used to verify cases and update if necessary. If this resulted in an imputed start date that was after the specified end date, then 01 Jan of the year of the end date was used, or the date of screening if this was later (if the latter imputation results in an end date that was earlier than the start date, then 01 Jan was used).

Imputation of partial end dates for AE and prior/concomitant medication:

- If only the month and year were specified, then the last day of the month was used.
- If only the year was specified, then 31 Dec of that year was used.
- If the stop date was completely unknown, the stop date was not imputed.
- If the AED medication stop date was completely missing on the History of AED eCRF page, then the stop date was imputed with the first brivaracetam dosing date -1. If the AED medication start date on the History of AED eCRF page was also completely missing, then 01 Jan of the year of the first brivaracetam dosing date was used as AED start date.

Imputation of the date of first diagnosis of epilepsy:

- If only the month and year were specified and the month and year of first dose was not the same as the month and year of the start date, then the first of the month was used.
- If only the month and year were specified and the month and year of first dose was the same as the month and year of the start date, then the date of first brivaracetam administration was used.
- If only the year was specified, and the year of first dose was not the same as the year of the start date, then 01 Jan of the year of the start date was used.
- If only the year was specified, and the year of first dose was the same as the year of the start date, then the date of first brivaracetam administration was used.
- Since eCRFs only collected year and month, and the start date was completely unknown, the date of first brivaracetam administration was used.
- If an imputed date of first diagnosis of epilepsy was less than the date of birth due to the application of imputation rules, then the date of first diagnosis of epilepsy was set to the date of birth for this derivation.

Except for the sensitivity analysis (described in Section 9.9.5), any missing seizure count was not considered seizure freedom.

9.9.5 Sensitivity analysis

Sensitivity analyses of seizure freedom at 3, 6, 9, and 12 months were performed at database lock using an alternate method for addressing missing seizure count as detailed below:

- A sensitivity analysis followed a less conservative approach in assessing seizure freedom. Calculation of seizure freedom now included missing seizure data where no reported seizures would also be considered seizure free, irrespective of whether other types of data were present at the same visit.

9.9.6 Amendments to the SAP

Per the SAP, certain analyses were originally planned to be presented by country. This was removed from the final analysis due to high variability in the number of enrolled patients between countries.

One amendment to the SAP was produced. This amendment is described in the following table.

SAP version	Approval date	Change	Rationale
1.0	30 May 2022	Not applicable	Original version
2.0	16 Oct 2023	1: Updates in Protocol Amendment 2.0 (24 Oct 2022) were incorporated to the SAP, including new protocol amendment version date, sample size, and Table 1-2 footnotes.	Based on the Protocol Amendment.
		2: Section 5.1 General Consideration: The decimal place of standard deviation was changed from 2 decimal places more than source data to 1 decimal place more than source data.	To follow UCB's standards.
		3: Section numbers from Section 5.3.2 to Section 5.3.5 were renumbered.	Section numbers in version 1.0 are not appropriate.
		4: Section 5.3.2: Seizure freedom for at least 6 consecutive months. The cutoff was changed to from 180 days to 136 days.	To align with the endpoint mapping window in the SAP (Section 5.1.1.1.4) per UCB's comments.

SAP version	Approval date	Change	Rationale
		5: Section 5.3.3.1 Sensitivity analysis of the primary variable. Removed sensitivity analysis of the primary variable.	It was determined a sensitivity analysis of the primary variable was not necessary. Added sensitivity analysis of the secondary endpoint (seizure freedom) to Section 5.4.2.1.1.
		6: Section 5.4.1.1.1: brivaracetam retention calculation was updated as: "Date of last administration of brivaracetam in Study Termination eCRF – date of first brivaracetam administration) +1.". "Date of Study Termination" was replaced by "Date of last administration of brivaracetam". In addition, more text was added to brivaracetam retention definition. Same for Section 5.4.1.1.2, Section 5.4.1.1.3, and Section 5.4.1.1.4.	There were some patients who terminated brivaracetam administration but didn't complete study termination form immediately (gap exists). Using "Date of last administration of brivaracetam" to calculate brivaracetam retention was more accurate than using "Date of Study Termination". Added more wordings to clarify the definition of brivaracetam retention.
		7: Section 5.4.2.3: Revised event definition and reformatted censoring rules of this section.	To clarify the definition of event and censor.
		8: Section 5.5.1.1.3.1: Removed "Final Score (Mean x Distress%)" from Table 5-2.	Stress score was not included for Total Score calculation, as described in the text of the SAP.

SAP version	Approval date	Change	Rationale
		9: Section 5.7: 28-day Baseline all types of POS frequency: Updated the subgroup categories as: 0, >0-<1, 1-5, >5-10, >10.	The original categories were ≤5, >5-10, >10. Breaking down by more categories to display more information.
		10: Section 6.1.1.2: Removed "For 28-Day Baseline frequency calculated values will round up into integer and classify into categories for any nonzero values."	No rounding was needed per team's decision. The percentage of patients with seizure frequency >0-<1 was added to the summary table.
		11. Section 6.1.4: AEDs grouping information was added.	These AEDs are with similar active substance.
		12: Section 6.1.5.3.1: The imputation rules for completely missing stop date were updated.	Imputation rules for the completely missing stop date impacted the AED classification (Prior vs Concomitant AED).

AED=antiepileptic drug; eCRF=electronic Case Report Form; POS=partial-onset seizures; SAP=statistical analysis plan.

9.10 Quality control

9.10.1 Monitoring

Monitoring of the study was delegated by UCB to a CRO. The CRO monitored the study to meet the CRO's monitoring standard operating procedures and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure were adequate.

In order to safeguard and assure data quality, a site management plan was developed that included details on site monitoring visits, site management by telephone, and source data verification.

A central monitoring approach was applied so monitoring activities were focused on the areas with the highest potential to impact data quality. Ongoing document review, data review, and analysis was performed remotely by UCB/the CRO to examine the data collected in order to check compliance and identify unusual data patterns, deviations from protocol, or missing or invalid data. On-site monitoring visits were performed on a for-cause basis.

The treating physician and his/her staff cooperated with UCB (or designee) and were available during the monitoring visits to answer questions sufficiently and to provide any missing information. The treating physician(s)/institution(s) permitted direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

All source documents should have been accurate, clear, unambiguous, permanent, and capable of being audited. They should have been made using some permanent form of recording (ink, typing, printing, optical disc).

9.10.2 Data handling

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and followed generally accepted research practices as described in EMA European Network of Centers for Pharmacoepidemiology and Pharmacovigilance Guide on Methodological Standards in Pharmacoepidemiology.

PDCFs were obtained and documented in accordance with local regulations, applicable data protection regulations, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

9.10.2.1 CRF completion

The treating physician or study personnel were responsible for reporting of accurate and complete data in the eCRFs and in all required reports promptly within the specified time.

Any change or correction to the eCRF after saving was accompanied by a reason for the change. Corrections made after the treating physician's review and approval (by means of a password/electronic signature) of the completed eCRF would have been reapproved by the treating physician. The treating physician maintained a list of personnel authorized to enter data into the eCRF.

9.10.2.2 Database entry and reconciliation

The data were entered into the eCRFs once and were subsequently verified. Data from eCRFs and the Helpilepsy application were received via external electronic file and entered or loaded into a validated electronic database using a CDMS. Computerized data cleaning checks were used in addition to manual review to check for discrepancies and to ensure consistency of the data.

Within this NIS, the Helpilepsy application was offered as a voluntary option to the participating sites and patients. The use of the Helpilepsy application within the study was limited to data collection on self-reported seizure frequency and patient-reported questionnaires.

An electronic audit trail system was maintained within the CDMS to track all data changes in the database once the data had been saved initially into the CDMS or electronically loaded. Regular backups of the electronic data were performed.

For reporting of an SAE, AESI, or pregnancy, the treating physician forwarded to UCB (or its representative) a duly completed Adverse Event Report form for NIS provided by UCB. Relevant information recorded on the Adverse Event Report form for NIS was entered into the global safety database of UCB.

9.10.2.3 Patient enrollment log/patient identification list

The patient's inclusion was recorded in the Patient Enrollment log.

The treating physician kept a Patient Identification Code list. This list remained with the treating physician and could be used for unambiguous identification of each patient.

Access to this list was granted only to members of staff, authorized persons of UCB (or designees), and the competent authorities. After the end of the study, the identification list remained with the physician.

The patient's consent date and inclusion in the study was recorded in the patient's medical record. These data identified the study and documented the dates of the patient's participation.

10 RESULTS

10.1 Participants

Enrolled patients were observed for approximately 12 months after the first dose of brivaracetam or until early termination.

10.1.1 Patient disposition

A total of 403 patients were enrolled at 62 sites across Germany (172 patients enrolled at 21 sites), Italy (110 patients enrolled at 19 sites), Spain (26 patients enrolled at 5 sites), France (87 patients enrolled at 13 sites), and Canada (8 patients enrolled at 4 sites) (Table 1.2). All 403 patients were included in the APD, 392 (97.3%) patients were included in the SS, and 304 (75.4%) patients were included in the PPS (Table 1.1).

Of the 392 patients in the SS, 298 (76.0%) completed the 12-month study period; 94 (24.0%) discontinued the study prematurely. The top 3 most commonly reported reasons for premature study termination were adverse event (34.0%), lost to follow up (27.7%), and lack of efficacy (18.1%). The 3 most commonly reported reasons for brivaracetam discontinuation were other intolerance (37.9%), lack of efficacy (25.8%), and other (25.8%). There were 311 (79.3%) patients being prescribed brivaracetam after exiting the study, per Post-Study Treatment Continuation captured in the eCRFs. There were no notable differences in patient disposition or discontinuation reasons between the SS and the PPS (Table 10-1).

Table 10-1: Disposition and discontinuation reasons (SS and PPS)

Disposition	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
During Study Treatment Period		
Started Study	392 (100)	304 (100)
Completed 12 Months	298 (76.0)	237 (78.0)
Discontinued the Study Prematurely	94 (24.0)	67 (22.0)
Primary Reason for Premature Study Termination	94 (24.0)	67 (22.0)
Adverse Event [a]	32 (34.0)	22 (32.8)
Lack of Efficacy [a]	17 (18.1)	12 (17.9)
Lost to Follow Up [a]	26 (27.7)	24 (35.8)
Disease Remission [a]	2 (2.1)	2 (3.0)
Consent Withdrawn by Patient [a]	5 (5.3)	3 (4.5)
Other [a]	12 (12.8)	4 (6.0)
Primary Reason for BRV Discontinuation	66 (16.8)	46 (15.1)
Behavioral Side Effects [b]	7 (10.6)	6 (13.0)

Table 10-1: Disposition and discontinuation reasons (SS and PPS)

Disposition	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Other Intolerance [b]	25 (37.9)	16 (34.8)
Lack of Efficacy [b]	17 (25.8)	12 (26.1)
Other [b]	17 (25.8)	12 (26.1)
Post-Study Treatment Continuation [c]	392 (100)	304 (100)
Patients being prescribed BRV after exiting the study [d]	311 (79.3)	245 (80.6)
Patients not being prescribed BRV after exiting the study [d]	68 (17.3)	48 (15.8)
Missing [d]	13 (3.3)	11 (3.6)

BRV=brivaracetam; PPS=Per Protocol Set; SS=Safety Set.
Note: Percentages were based on the number of patients in the SS or PPS. A patient who completed the study was defined as someone who had completed both Baseline Visit and Follow Up Period (through Month 12).
Note: Two patients terminated the study with reason for discontinuation recorded as "lack of efficacy"; however, they were recorded in the Adverse Events eCRF as "Did Adverse Event Lead to Dropout = Yes".
a Percentages were calculated out of the number of patients with premature study termination during the study.
b Percentages were calculated out of the number of patients with discontinuation of brivaracetam during the study.
c The number of Post-Study Treatment Continuation included patients with 12 months completion and those who discontinued the study prematurely.
d Percentages were calculated out of the number of patients with data in the Post-Study Treatment Continuation eCRF.
Source: Table 1.3.1, Table 1.3.2

Patient attendance by eCRF visit is summarized for the SS in Table 1.4.1 and for the PPS in Table 1.5.1. A summary of analysis visits after mapping patients' last visit date to the corresponding timepoint according to the mapping window (Table 9-2) is presented for the SS and the PPS in Table 10-2.

Table 10-2: Patients attendance by analysis visit (SS and PPS)

Visit	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Visit 1 (Baseline)	392 (100)	304 (100)
Visit 2 (Month 3)	344 (87.8)	269 (88.5)
Visit 3 (Month 6)	314 (80.1)	248 (81.6)
Visit 4 (Month 9)	298 (76.0)	237 (78.0)
Visit 5 (Month 12)	299 (76.3)	238 (78.3)

eCRF=electronic Case Report Form; PPS=Per Protocol Set; SS=Safety Set.

Note: This table is the summary of analysis visits after mapping. The visit mapping window varies among endpoints. This table combines the visit mapping results of different endpoints.
Note: Percentages were based on the number of patients who completed the Baseline Visit.
Note: A patient was considered to have attended a visit if a visit date was present and within the mapping window of the corresponding timepoint.
Note: The number of patients who completed Visit 5 (Month 12) was based on the analysis visit after mapping (Table 9-2), which is different from the number of patients "Completed 12 months" in Table 10-1 based on patient status at Study Termination eCRF.
Source: Table 1.4.2, Table 1.5.2

10.1.2 Important protocol deviations

Among the SS, 96 (24.5%) patients had at least 1 important protocol deviation. Sixty-five (16.6%) patients had study drug-related important protocol deviations (brivaracetam dosing not according to SmPC), 79 (20.2%) patients had at least 1 selection criteria deviation, 21 (5.4%) patients had incorrect treatment or dose, and 1 (0.3%) patient had procedural noncompliance.

There were 88 (22.4%) patients excluded from the PPS due to important protocol deviations. The most common important protocol deviations leading to exclusion from the PPS were selection criteria deviation (18.4%) and brivaracetam dosing not according to SmPC recommendations (16.6%) (Table 3.1). A patient could have had more than 1 protocol deviation.

10.2 Descriptive data

10.2.1 Demographic characteristics

At Baseline, the mean (SD) age of all patients was 44.9 (17.4) years for the SS and 46.1 (17.6) years for the PPS. Around half of patients were male (52.0% for the SS; 53.3% for the PPS). The majority of patients did not use the Helpilepsy application (65.3% for the SS; 69.7% for the PPS) (Table 10-3).

Additional demographic details are provided in Table 2.1.2. Compared with the SS, there were no notable differences in demographics or Baseline characteristics observed in the APD or the PPS (Table 2.1.1 and Table 2.1.3).

Table 10-3: Demographics and Baseline characteristics (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Age at Visit 1 (years)			
	Mean (SD)	44.9 (17.4)	46.1 (17.6)
	Median (Q1, Q3)	43.0 (30.0, 57.0)	45.0 (31.0, 59.0)
	IQR	27.0	28.0
	Min, Max	18, 86	18, 85
Age category			
<18 years [a]	n (%)	0	0
18 to <45 years	n (%)	202 (51.5)	150 (49.3)

Table 10-3: Demographics and Baseline characteristics (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
45 to <65 years	n (%)	127 (32.4)	100 (32.9)
≥65 years	n (%)	63 (16.1)	54 (17.8)
Gender			
Male	n (%)	204 (52.0)	162 (53.3)
Female	n (%)	188 (48.0)	142 (46.7)
Education			
Less than high school	n (%)	136 (34.7)	110 (36.2)
High school graduate	n (%)	139 (35.5)	110 (36.2)
Some college, no degree	n (%)	27 (6.9)	21 (6.9)
College degree	n (%)	48 (12.2)	32 (10.5)
Postgraduate or professional degree	n (%)	39 (9.9)	29 (9.5)
Missing	n (%)	3 (0.8)	2 (0.7)
Current professional status			
Full time employed	n (%)	151 (38.5)	111 (36.5)
Part time employed	n (%)	31 (7.9)	28 (9.2)
Unemployed	n (%)	210 (53.1)	164 (53.9)
Missing	n (%)	2 (0.5)	1 (0.3)
Part time/unemployed reason			
Epilepsy	n (%)	70 (29.3)	59 (30.7)
Retired	n (%)	69 (28.9)	61 (31.8)
Student	n (%)	31 (13.0)	22 (11.5)
Seeking work (or able to work if a job were available	n (%)	21 (8.8)	14 (7.3)
House keeping	n (%)	14 (5.9)	10 (5.2)
Other	n (%)	34 (14.2)	26 (13.5)
Helpilepsy user [b]			
Yes	n (%)	136 (34.7)	92 (30.3)
No	n (%)	256 (65.3)	212 (69.7)

eCRF=electronic Case Report Form; IQR=interquartile range; Max=maximum; Min=minimum; PPS=Per Protocol Set; Q1=25th percentile; Q3=75th percentile; SD=standard deviation; SS=Safety Set.

[a] Inclusion criteria required that patients were 18 years old or older; however, this row was included in case there was a patient with age less than 18 in the cohort.

[b] Helpilepsy users were defined as patients who selected "Yes" to "Will the patient use the Helpilepsy application?" on the Baseline eCRF and also any patients who selected "No" and provided Helpilepsy data; 2 patients (EP0103-531-12014 and EP0103-533-12299) responded with "Will the patient use the Helpilepsy application? = No" in the Patient Identification eCRF and used Helpilepsy later during the study.

Source: Table 2.1.2, Table 2.1.3

10.2.2 Baseline characteristics

10.2.2.1 Medical history conditions

Among the SS, 291 (74.2%) patients reported previous medical history conditions (including COVID-19 infection). The most commonly reported medical history conditions (≥10% of patients) summarized by SOC were psychiatric disorders (29.1%), nervous system disorders (26.3%), vascular disorders (21.7%), and metabolism and nutrition disorders (11.2%) (Table 4.1.1).

The reported medical history conditions in the PPS were comparable with the SS (Table 4.1.2).

10.2.2.2 Disease characteristics

History of epilepsy for all patients for the SS and the PPS is presented below in Table 10-4. The median time since first diagnosis of epilepsy for the SS was 8.37 years, and 175 (44.6%) patients had a time since first diagnosis of epilepsy of >10 years. The median percent of life with epilepsy was 21.68%. The patients' history of epilepsy was comparable between the SS and the PPS.

Table 10-4: History of epilepsy (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Time since first diagnosis of epilepsy (years)	n	389	301
	Mean (SD)	13.04 (13.19)	13.20 (13.53)
	Median (Q1, Q3)	8.37 (3.28, 19.65)	8.57 (3.24, 20.23)
	IQR	16.37	17.00
	Min, Max	0.3, 63.6	0.3, 63.6
Time since first diagnosis of epilepsy	n	392	304
0-<1 year	n (%)	32 (8.2)	24 (7.9)
1-<5 years	n (%)	113 (28.8)	94 (30.9)
5-10 years	n (%)	69 (17.6)	47 (15.5)
>10 years	n (%)	175 (44.6)	136 (44.7)
Missing	n (%)	3 (0.8)	3 (1.0)

Table 10-4: History of epilepsy (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Age at the time of first diagnosis of epilepsy (years)	n	389	301
	Mean (SD)	31.87 (20.14)	32.86 (20.80)
	Median (Q1, Q3)	27.83 (16.55, 47.92)	28.78 (16.55, 49.37)
	IQR	31.37	32.82
	Min, Max	0.0, 82.6	0.0, 82.6
Percent of life with epilepsy (%)	n	389	301
	Mean (SD)	31.46 (28.57)	31.30 (28.59)
	Median (Q1, Q3)	21.68 (6.73, 49.65)	21.38 (6.65, 50.70)
	IQR	42.93	44.05
	Min, Max	0.4, 100.0	0.4, 100.0

IQR=interquartile range; Max=maximum; Min=minimum; PPS=Per Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set.
Source: Table 2.2.1, Table 2.2.2

A summary of Baseline seizure frequency is presented in Table 10-5.

Of the 392 patients in the SS, 381 (97.2%) patients reported any Baseline POS, 4 (1.0%) patients reported none, and 7 (1.8%) patients had missing data. Among these 381 patients, the median (Q1, Q3) 28-day Baseline POS frequency (based on the 3 months prior to Visit 1) was 2.00 (0.67, 4.00). Baseline POS with secondary generalization were reported by 143 (36.5%) patients, 243 (62.0%) patients reported none, and 6 (1.5%) patients had missing data. Among these 143 patients, the median (Q1, Q3) 28-day Baseline POS with secondary generalization frequency (based on the 3 months prior to Visit 1) was 0.67 (0.33, 1.00).

Per selection criteria, only patients with any Baseline seizures frequency were included in the PPS. Overall, Baseline seizure frequency was comparable between the SS and the PPS.

Table 10-5: Baseline seizure frequency (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Any Baseline seizures	n	392	304
Yes	n (%)	386 (98.5)	300 (98.7)
No	n (%)	2 (0.5)	0
Missing	n (%)	4 (1.0)	4 (1.3)
If yes, 28-day Baseline all types of seizure frequency [a]	n	386	300

Table 10-5: Baseline seizure frequency (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
	Mean (SD)	6.37 (21.72)	7.12 (24.36)
	Median (Q1, Q3)	2.00 (0.67, 4.00)	2.00 (0.83, 4.50)
	IQR	3.33	3.67
	Min, Max	0.3, 300.0	0.3, 300.0
28-day Baseline all types of seizure frequency	n	388	300
0	n (%)	2 (0.5)	0
>0 to <1	n (%)	104 (26.8)	75 (25.0)
1-5	n (%)	206 (53.1)	161 (53.7)
>5 to 10	n (%)	32 (8.2)	27 (9.0)
>10	n (%)	44 (11.3)	37 (12.3)
Any Baseline POS	n	392	304
Yes	n (%)	381 (97.2)	298 (98.0)
No	n (%)	4 (1.0)	0
Missing	n (%)	7 (1.8)	6 (2.0)
If yes, 28-day Baseline POS frequency [a]	n	381	298
	Mean (SD)	6.26 (21.72)	6.95 (24.29)
	Median (Q1, Q3)	2.00 (0.67, 4.00)	2.00 (0.67, 4.00)
	IQR	3.33	3.33
	Min, Max	0.3, 300.0	0.3, 300.0
28-day Baseline POS frequency	n	385	298
0	n (%)	4 (1.0)	0
>0 to <1	n (%)	106 (27.5)	79 (26.5)
1-5	n (%)	202 (52.5)	157 (52.7)
>5 to 10	n (%)	30 (7.8)	26 (8.7)
>10	n (%)	43 (11.2)	36 (12.1)
Any Baseline POS with secondary generalization	n	392	304
Yes	n (%)	143 (36.5)	117 (38.5)
No	n (%)	243 (62.0)	182 (59.9)

Table 10-5: Baseline seizure frequency (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Missing	n (%)	6 (1.5)	5 (1.6)
If yes, 28-day Baseline POS with secondary generalization frequency	n	143	117
	Mean (SD)	1.34 (2.87)	1.24 (2.62)
	Median (Q1, Q3)	0.67 (0.33, 1.00)	0.67 (0.33, 1.00)
	IQR	0.67	0.67
	Min, Max	0.3, 20.0	0.3, 16.7
28-day Baseline POS with secondary generalization frequency	n	388	301
0	n (%)	245 (63.1)	184 (61.1)
>0 to <1	n (%)	97 (25.0)	80 (26.6)
1-5	n (%)	41 (10.6)	33 (11.0)
>5 to 10	n (%)	0	0
>10	n (%)	5 (1.3)	4 (1.3)
Any Baseline of all types of generalized onset seizure frequency	n	392	304
Yes	n (%)	25 (6.4)	18 (5.9)
No	n (%)	360 (91.8)	280 (92.1)
Missing	n (%)	7 (1.8)	6 (2.0)
If yes, 28-day all types of generalized onset seizure frequency	n	25	18
	Mean (SD)	2.20 (5.50)	2.52 (6.44)
	Median (Q1, Q3)	0.67 (0.33, 1.00)	0.67 (0.33, 1.00)
	IQR	0.67	0.67
	Min, Max	0.3, 28.0	0.3, 28.0
Frequency of all types of generalized onset seizure frequency	n	388	301
0	n (%)	363 (93.6)	283 (94.0)
>0 to <1	n (%)	15 (3.9)	10 (3.3)
1-5	n (%)	9 (2.3)	7 (2.3)

Table 10-5: Baseline seizure frequency (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
>5 to 10	n (%)	0	0
>10	n (%)	1 (0.3)	1 (0.3)

IQR=interquartile range; Max=maximum; Min=minimum; POS=partial-onset seizure; PPS=Per Protocol Set; Q1=25th percentile; Q3=75th percentile; SD=standard deviation; SS=Safety Set.
Note: Percentages were calculated using the corresponding category count as the denominator.
Note: Patients with an answer of "Yes" for the leading question of "Did the patient experience any seizure during the 3 months prior to Baseline Visit?" and with available nonzero seizure count number for the corresponding type of seizure were classified as "Yes" in this table. If the answer was "Yes" for the leading question but the seizure count was missing, they were classified as "Missing". If the answer was "No" for the leading question or if the seizure count was 0 (regardless of the answer for leading question), they were classified as "No".
[a] Baseline seizure frequency was based on the 3 months prior to Visit 1 (Baseline) to estimate the frequency per 28 days.
Source: Table 2.4.1, Table 2.4.2

The etiology of epilepsy among patients in this study is provided for the SS in Table 2.5.1 and for the PPS in Table 2.5.2. Patients could report more than 1 etiology. There were 202 (51.5%) patients in the SS that had an unknown etiology, and 189 (48.2%) patients had a known etiology. Among the known etiologies, the most common (≥5% of patients) were cranial trauma (7.7%), cortical dysplasia/dysgenesis (6.1%), primary degeneration lesion (6.1%), and other (8.9%). Epilepsy etiology in the PPS was comparable with the SS.

Among the SS, the most common reasons for initiation of brivaracetam were lack of efficacy of current treatment (89.8%) and behavioral side effects to current AED (13.3%) (Table 2.3.1). This was consistent with the PPS (Table 2.3.2).

10.2.2.3 Prior and concomitant medications

10.2.2.3.1 Lifetime AEDs

The number of lifetime AEDs (a sum of the prior AEDs and concomitant AEDs at brivaracetam initiation, excluding benzodiazepines or other rescue medications used short term per physician discretion and any AEDs not taken for at least 7 consecutive days) by prior AEDs and concomitant AEDs at brivaracetam initiation is presented for the SS and the PPS in Table 5.1.1 and Table 5.1.2, respectively. The classification of a drug as an AED or non-AED was done based on the reported indication.

In the SS, the percentages of patients who had 1, 2, or 3 lifetime AEDs at brivaracetam initiation were 29.6%, 41.1%, or 23.7%, respectively. Results were comparable in the PPS (32.2% of patients had 1 lifetime AED, 40.1% had 2, and 26.0% had 3). There were 16 (4.1%) patients in the SS who had >3 lifetime AEDs and, per definition, were not included in the PPS. The median (Q1, Q3) number of lifetime AEDs was 2.0 (1.0, 3.0) for the SS and the PPS (Table 5.3.7 and Table 5.3.8).

10.2.2.3.2 Prior medications

The number of prior AEDs (defined as AEDs discontinued prior to the date of first brivaracetam administration) by number of use categories are presented for the SS and the PPS in Table 5.1.3

and Table 5.1.4, respectively. Of the 392 patients in the SS, 207 (52.8%) patients documented prior AEDs. The percentages of patients who had 1 or 2 prior AEDs were 38.0% and 12.2%, respectively. Results were comparable in the PPS, with 152 (50.0%) patients documenting prior AEDs; 39.1% and 10.5% documented 1 or 2 prior AEDs, respectively.

The most common (≥5% of patients) prior AEDs medications are presented for the SS and the PPS in Table 10-6. The median (Q1, Q3) number of prior AEDs was 1.0 (0.0, 1.0) for the SS and 0.5 (0.0, 1.0) for the PPS (Table 5.3.7 and Table 5.3.8).

Table 10-6: Prior AED medications occurring in ≥5% of SS or PPS patients (SS and PPS)

WHODD SEP/2020 B3 PT	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Any Prior AED Medications	207 (52.8)	152 (50.0)
Levetiracetam	87 (22.2)	64 (21.1)
Carbamazepine	47 (12.0)	29 (9.5)
Valproate	35 (8.9)	21 (6.9)
Lamotrigine	31 (7.9)	21 (6.9)

AED=antiepileptic drug; PPS=Per Protocol Set; PT=preferred term; SAP=statistical analysis plan; SS=Safety Set; WHODD=World Health Organization Drug Dictionary.
Note: Prior AEDs were defined as AEDs discontinued prior to the date of first brivaracetam administration.
Note: AEDs with similar active substance were grouped and summarized together as per SAP Section 6.1.4. Combination AEDs were not considered for grouping.
Source: Table 5.2.1, Table 5.2.2

A total of 26 (6.6%) patients in the SS and 18 (5.9%) patients in the PPS had any prior non-AED medications (defined as non-AEDs discontinued prior to the date of first brivaracetam administration) (Table 5.2.3 and Table 5.2.4).

10.2.2.3.3 Concomitant medications

Concomitant AEDs at brivaracetam initiation

The number of concomitant AEDs at brivaracetam initiation (defined as those AEDs being taken on the same day as the first brivaracetam administration) by number of AED use categories are presented for the SS and the PPS in Table 5.1.3 and Table 5.1.4, respectively. Of the 392 patients in the SS, 391 (99.7%) patients had concomitant AEDs at brivaracetam initiation. The percentages of patients who had 1 or 2 concomitant AEDs at brivaracetam initiation were 61.5% and 32.9%, respectively. The results were comparable in the PPS, with 194 (63.8%) patients reporting 1 concomitant AED and 98 (32.2%) patients reporting 2 concomitant AEDs at brivaracetam initiation.

The median (Q1, Q3) number of concomitant AEDs at brivaracetam initiation was 1.0 (1.0, 2.0) for the SS and the PPS (Table 5.3.7 and Table 5.3.8). The most common (≥5% of patients) concomitant AED medications at brivaracetam initiation are presented by number of concomitant AEDs for the SS and for the PPS in Table 10-7.

Table 10-7: Concomitant AED medications at brivaracetam initiation in ≥5% of SS or PPS patients (SS and PPS)

WHODD SEP/2020 B3 PT	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Number of concomitant AEDs at BRV initiation: 1		
Any Concomitant AED Medications	241 (61.5)	194 (63.8)
Lamotrigine	62 (15.8)	48 (15.8)
Lacosamide	51 (13.0)	41 (13.5)
Levetiracetam	34 (8.7)	33 (10.9)
Carbamazepine	31 (7.9)	24 (7.9)
Eslicarbazepine	21 (5.4)	18 (5.9)
Number of concomitant AEDs at BRV initiation: 2		
Any Concomitant AED Medications	129 (32.9)	98 (32.2)
Lacosamide	50 (12.8)	42 (13.8)
Levetiracetam	43 (11.0)	33 (10.9)
Lamotrigine	40 (10.2)	28 (9.2)
Valproate	22 (5.6)	15 (4.9)

AED=antiepileptic drug; BRV=brivaracetam; PPS=Per Protocol Set; PT=preferred term; SAP=statistical analysis plan; SS=Safety Set; WHODD=World Health Organization Drug Dictionary.
Note: The concomitant AEDs at brivaracetam initiation were defined as those AEDs being taken on the same day as first brivaracetam administration.
Note: AEDs with similar active substance were grouped and summarized together as per SAP Section 6.1.4. Combination AEDs were not considered for grouping.
Source: Table 5.3.3, Table 5.3.4

Any concomitant AEDs

The median (Q1, Q3) number of concomitant AEDs (defined as AED medications taken at least 1 day in common with the study medication) was 1.0 (1.0, 2.0) for the SS and the PPS (Table 5.3.7 and Table 5.3.8).

The most common (≥5% of patients) concomitant AED medications for the SS and the PPS are presented below in Table 10-8.

Table 10-8: Any Concomitant AED medications in ≥5% of SS or PPS patients (SS and PPS)

WHODD SEP/2020 B3 PT	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Any concomitant AED medications	391 (99.7)	304 (100.0)

Table 10-8: Any Concomitant AED medications in ≥5% of SS or PPS patients (SS and PPS)

WHODD SEP/2020 B3 PT	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Lacosamide	121 (30.9)	93 (30.6)
Lamotrigine	116 (29.6)	84 (27.6)
Levetiracetam	88 (22.4)	72 (23.7)
Carbamazepine	57 (14.5)	45 (14.8)
Eslicarbazepine	41 (10.5)	33 (10.9)
Valproate	39 (9.9)	29 (9.5)
Benzodiazepine	30 (7.7)	16 (5.3)
Oxcarbazepine	23 (5.9)	11 (3.6)
Perampanel	23 (5.9)	16 (5.3)

AED=antiepileptic drug; PPS=Per Protocol Set; PT=preferred term; SAP=statistical analysis plan; SS=Safety Set; WHODD=World Health Organization Drug Dictionary.
Note: Concomitant AEDs are AED medications taken at least 1 day in common with the study medication.
Note: AEDs with similar active substance were grouped and summarized together as per SAP section 6.1.4. Combination AEDs were not considered for grouping.
Source: Table 5.3.1, Table 5.3.2

Any concomitant non-AEDs

A total of 204 (52.0%) patients in the SS and 155 (51.0%) patients in the PPS reported any concomitant non-AED medications taken during the study (Table 5.3.5 and Table 5.3.6). By pharmacological subgroup (level 3), the top 3 most common concomitant non-AED medications taken by patients were antidepressants (13.5% for the SS and the PPS), antithrombotic agents (11.0% for the SS; 11.5% for the PPS), and lipid modifying agents, plain (7.9% for the SS; 8.9% for the PPS).

10.3 Main results

10.3.1 Primary variable

10.3.1.1 Seizure freedom for at least 6 consecutive months over a 12-month observation period

A summary of seizure freedom for at least 6 consecutive months during the study is presented for the SS and the PPS in Table 10-9. In the SS, 125 (41.9%) of 298 patients were seizure free for at least 6 consecutive months over the 12-month observation period. In the PPS, 100 (42.2%) of 237 patients were seizure free for at least 6 consecutive months over a 12-month observation period.

Table 10-9: Seizure freedom for at least 6 consecutive months (SS and PPS)

Variable	All patients (SS) N=392 n/Nsub (%) 95% CI [a]	All patients (PPS) N=304 n/Nsub (%) 95% CI [a]
Overall Number of Patients with at Least 6 Consecutive Months of Seizure Freedom (during 12 months) [b]	125/298 (41.9) (36.3, 47.8)	100/237 (42.2) (35.8, 48.8)
Number of Patients with 6 Months Seizure Freedom		
from Baseline to Visit 3 (Month 6)	81/292 (27.7) (22.7, 33.3)	65/233 (27.9) (22.2, 34.1)
from Visit 2 (Month 3) to Visit 4 (Month 9)	82/262 (31.3) (25.7, 37.3)	65/212 (30.7) (24.5, 37.3)
from Visit 3 (Month 6) to Visit 5 (Month 12)	90/249 (36.1) (30.2, 42.4)	71/199 (35.7) (29.0, 42.8)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage was based on the denominator for number of patients who completed the respective 2 consecutive visits with nonmissing data and the visit date of 2 or 3 consecutive visits must have been at least 6 months (≥136 days) apart (Nsub).
Note: Any missing seizure count between visits was not considered seizure freedom.
[a] 95% CI for percentage.
[b] The numerator was defined as patients with at least 6 consecutive months of seizure freedom, regardless of completion of the study. The visit date of 2 or 3 consecutive visits must have been at least 6 months (≥136 days) apart.
Source: Table 6.1.1.1, Table 6.1.1.2

10.3.1.1.1 Seizure freedom for at least 6 consecutive months over a 12-month observation period: completers

The number of patients with at least 6 consecutive months of seizure freedom among those patients who completed the 12 month visit is presented in Table 10-10. In the SS, 120 (43.5%) of 276 patients were seizure free for at least 6 consecutive months, and in the PPS, 95 (42.8%) of 222 patients were seizure free for at least 6 consecutive months. Seizure freedom results of completers are similar to the main analysis.

Table 10-10: Seizure freedom for at least 6 consecutive months (completer) (SS and PPS)

Variable	All patients (SS) N=298 [a] n/Nsub (%) 95% CI [b]	All patients (PPS) N=237 [a] n/Nsub (%) 95% CI [b]
Overall number of patients with at least 6 consecutive months of seizure freedom (during 12 months) [c]	120/276 (43.5) (37.5, 49.6)	95/222 (42.8) (36.2, 49.6)
Number of Patients with 6 Months Seizure Freedom		
from Baseline to Visit 3 (Month 6)	77/270 (28.5) (23.2, 34.3)	61/218 (28.0) (22.1, 34.4)
from Visit 2 (Month 3) to Visit 4 (Month 9)	80/252 (31.7) (26.0, 37.9)	63/204 (30.9) (24.6, 37.7)
from Visit 3 (Month 6) to Visit 5 (Month 12)	90/248 (36.3) (30.3, 42.6)	71/198 (35.9) (29.2, 43.0)

eCRF=electronic case report form; CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage was based on the denominator for number of patients who completed the respective 2 consecutive visits with nonmissing data and the visit date of 2 or 3 consecutive visits must have been at least 6 months (≥136 days) apart (Nsub).
Note: Any missing seizure count between visits was not considered seizure freedom.
Note: This table only includes patients who completed approximately 12 months of the study (Completer).
[a] Overall number of patients who completed the treatment period of approximately 12 months was based on the number of patients with the status of "Completed" in the Study Termination eCRF.
[b] 95% CI for percentage.
[c] The numerator was defined as patients with at least 6 consecutive months of seizure freedom. The visit date of 2 or 3 consecutive visits must have been at least 6 months (≥136 days) apart.
Source: Table 6.1.2.1, Table 6.1.2.2

10.3.1.1.2 Subgroup analysis

The overall number of patients with at least 6 consecutive months of seizure freedom (over the approximately 12-month study period) within each subgroup is presented in Table 10-11. A higher percentage of patients was seizure free for at least 6 consecutive months in subgroups with 1 to 2 lifetime AEDs, with brivaracetam in first or second adjunctive treatment lines, and Baseline POS frequency of ≤5. There were no meaningful differences between the SS and the PPS.

Table 10-11: Overall number of patients with at least 6 consecutive months of seizure freedom (during 12 months) by subgroup (SS and PPS)

Subgroup	All patients (SS) N=392 n/Nsub (%) [a] 95% CI [b]	All patients (PPS) N=304 n/Nsub (%) [a] 95% CI [b]
Number of lifetime AEDs		
1	42/88 (47.7) (37.0, 58.6)	33/75 (44.0) (32.5, 55.9)
2	56/124 (45.2) (36.2, 54.3)	45/94 (47.9) (37.5, 58.4)
3	23/74 (31.1) (20.8, 42.9)	20/64 (31.3) (20.2, 44.1)
Number of concomitant AEDs		
1	78/177 (44.1) (36.6, 51.7)	63/148 (42.6) (34.5, 51.0)
2	38/98 (38.8) (29.1, 49.2)	31/74 (41.9) (30.5, 53.9)
3	7/18 (38.9) (17.3, 64.3)	5/13 (38.5) (13.9, 68.4)
Treatment line in adjunctive therapy		
First	67/145 (46.2) (37.9, 54.7)	52/115 (45.2) (35.9, 54.8)
Second	45/109 (41.3) (31.9, 51.1)	37/85 (43.5) (32.8, 54.7)
Third	11/40 (27.5) (14.6, 43.9)	11/36 (30.6) (16.3, 48.1)
28-day Baseline all types POS frequency		
>0 to <1	48/84 (57.1) (45.9, 67.9)	38/63 (60.3) (47.2, 72.4)
1 to 5	69/158 (43.7) (35.8, 51.8)	55/125 (44.0) (35.1, 53.2)
>5 to 10	4/22 (18.2) (5.2, 40.3)	4/21 (19.0) (5.4, 41.9)
>10	4/31 (12.9) (3.6, 29.8)	3/27 (11.1) (2.4, 29.2)

AED=antiepileptic drug; CI=confidence interval; POS=partial-onset seizure; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage was based on the denominator for number of patients who completed the respective 2 consecutive visits with nonmissing data and the visit date of 2 or 3 consecutive visits must have been at least 6 months (≥136 days) apart (Nsub).
Note: Any missing seizure count between visits was not considered seizure freedom.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Lifetime AEDs were defined as a sum of the prior AEDs and concomitant AEDs medications at brivaracetam initiation. An AED was counted as a lifetime AED if it was used for the treatment of seizures for at least 7 consecutive days (1 week) any time before brivaracetam initiation (excluding benzodiazepines or other rescue medications used short term per physician discretion).
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
[a] The numerator was defined as patients with at least 6 consecutive months of seizure freedom, regardless of completion of the study. The visit date of 2 or 3 consecutive visits must have been at least 6 months (≥136 days) apart.
[b] 95% CI for percentage.
Source: Table 6.1.1.3, Table 6.1.1.4, Table 6.1.1.5, Table 6.1.1.6, Table 6.1.1.7, Table 6.1.1.8, Table 6.1.1.9, Table 6.1.1.10

10.3.2 Secondary variables

10.3.2.1 Brivaracetam retention at 3, 6, 9, and 12 months

The adjunctive brivaracetam retention rates at 3, 6, 9, and 12 months are presented for the SS and the PPS in Table 10-12. Overall, retention remained high throughout the study. The 12-month retention rate was 75.5% in the SS and 77.0% in the PPS.

Table 10-12: Brivaracetam retention at 3/6/9/12 months (SS and PPS)

Variable	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
3 Months Retention	352/392 (89.8)	276/304 (90.8)
95% CI for percentage	(86.4, 92.6)	(87.0, 93.8)
6 Months Retention	322/392 (82.1)	252/304 (82.9)
95% CI for percentage	(78.0, 85.8)	(78.2, 87.0)
9 Months Retention	307/392 (78.3)	243/304 (79.9)
95% CI for percentage	(73.9, 82.3)	(75.0, 84.3)
12 Months Retention	296/392 (75.5)	234/304 (77.0)
95% CI for percentage	(70.9, 79.7)	(71.8, 81.6)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: n is the number of patients with brivaracetam retention at the corresponding visit. The windows for retention from first brivaracetam dosing to the last brivaracetam administration date were ≥80 days, ≥170 days, ≥260 days, and ≥330 days, respectively, for the visits of 3/6/9/12 months.
Note: Percentage is based on the number of patients in the SS or the PPS.
Source: Table 6.2.1, Table 6.2.2

10.3.2.1.1 Subgroup analysis

The adjunctive brivaracetam retention rates at 3, 6, 9, and 12 months within each subgroup are presented in Table 10-13, Table 10-14, Table 10-15, and Table 10-16.

Retention rates were generally high across the subgroups shown in these tables, specifically in subgroups with fewer lifetime AEDs, fewer concomitant AEDs, earlier treatment lines, and lower Baseline POS frequency.

Retention rate was relatively low in the subgroup with >3 lifetime AEDs in the SS, possibly due to more refractory disease. Subgroups with small sample sizes should be interpreted with caution.

Table 10-13: Brivaracetam retention at 3/6/9/12 months by subgroup: lifetime AEDs (SS and PPS)

Retention	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of lifetime AEDs: 1		
3 Months Retention 95% CI for percentage	104/116 (89.7) (82.6, 94.5)	88/98 (89.8) (82.0, 95.0)
6 Months Retention 95% CI for percentage	96/116 (82.8) (74.6, 89.1)	81/98 (82.7) (73.7, 89.6)
9 Months Retention 95% CI for percentage	93/116 (80.2) (71.7, 87.0)	79/98 (80.6) (71.4, 87.9)
12 Months Retention 95% CI for percentage	91/116 (78.4) (69.9, 85.5)	77/98 (78.6) (69.1, 86.2)
Number of lifetime AEDs: 2		
3 Months Retention 95% CI for percentage	149/161 (92.5) (87.3, 96.1)	113/122 (92.6) (86.5, 96.6)
6 Months Retention 95% CI for percentage	136/161 (84.5) (77.9, 89.7)	101/122 (82.8) (74.9, 89.0)
9 Months Retention 95% CI for percentage	131/161 (81.4) (74.5, 87.1)	99/122 (81.1) (73.1, 87.7)
12 Months Retention 95% CI for percentage	126/161 (78.3) (71.1, 84.4)	95/122 (77.9) (69.5, 84.9)

Table 10-13: Brivaracetam retention at 3/6/9/12 months by subgroup: lifetime AEDs (SS and PPS)

Retention	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of lifetime AEDs: 3		
3 Months Retention 95% CI for percentage	82/93 (88.2) (79.8, 93.9)	70/79 (88.6) (79.5, 94.7)
6 Months Retention 95% CI for percentage	75/93 (80.6) (71.1, 88.1)	66/79 (83.5) (73.5, 90.9)
9 Months Retention 95% CI for percentage	69/93 (74.2) (64.1, 82.7)	61/79 (77.2) (66.4, 85.9)
12 Months Retention 95% CI for percentage	65/93 (69.9) (59.5, 79.0)	58/79 (73.4) (62.3, 82.7)
Number of lifetime AEDs: >3		
3 Months Retention 95% CI for percentage	11/16 (68.8) (41.3, 89.0)	0/0 (NC, NC)
6 Months Retention 95% CI for percentage	10/16 (62.5) (35.4, 84.8)	0/0 (NC, NC)
9 Months Retention 95% CI for percentage	9/16 (56.3) (29.9, 80.2)	0/0 (NC, NC)
12 Months Retention 95% CI for percentage	9/16 (56.3) (29.9, 80.2)	0/0 (NC, NC)

AED=antiepileptic drug; CI=confidence interval; NC=not calculated; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: n is the number of patients with brivaracetam retention at the corresponding visit. The windows for retention from first brivaracetam dosing to the last brivaracetam administration date were ≥80 days, ≥170 days, ≥260 days, and ≥330 days, respectively, for the visits of 3/6/9/12 months. Nsub is the number of patients in the corresponding lifetime AED category.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Lifetime AEDs were defined as a sum of the prior AEDs and concomitant AEDs medications at brivaracetam initiation. An AED was counted as a lifetime AED if it was used for the treatment of seizures for at least 7 consecutive days (1 week) any time before brivaracetam initiation (excluding benzodiazepines or other rescue medications used short term per physician discretion).
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.2.3, Table 6.2.4

Table 10-14: Brivaracetam retention at 3/6/9/12 months by subgroup: concomitant AEDs (SS and PPS)

Retention	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of concomitant AEDs: 1		
3 Months Retention 95% CI for percentage	208/229 (90.8) (86.3, 94.2)	171/187 (91.4) (86.5, 95.0)
6 Months Retention 95% CI for percentage	189/229 (82.5) (77.0, 87.2)	156/187 (83.4) (77.3, 88.4)
9 Months Retention 95% CI for percentage	182/229 (79.5) (73.7, 84.5)	152/187 (81.3) (74.9, 86.6)
12 Months Retention 95% CI for percentage	178/229 (77.7) (71.8, 82.9)	148/187 (79.1) (72.6, 84.7)
Number of concomitant AEDs: 2		
3 Months Retention 95% CI for percentage	117/131 (89.3) (82.7, 94.0)	88/99 (88.9) (81.0, 94.3)
6 Months Retention 95% CI for percentage	107/131 (81.7) (74.0, 87.9)	80/99 (80.8) (71.7, 88.0)
9 Months Retention 95% CI for percentage	101/131 (77.1) (68.9, 84.0)	76/99 (76.8) (67.2, 84.7)
12 Months Retention 95% CI for percentage	96/131 (73.3) (64.8, 80.6)	72/99 (72.7) (62.9, 81.2)
Number of concomitant AEDs: 3		
3 Months Retention 95% CI for percentage	22/27 (81.5) (61.9, 93.7)	15/16 (93.8) (69.8, 99.8)
6 Months Retention 95% CI for percentage	21/27 (77.8) (57.7, 91.4)	14/16 (87.5) (61.7, 98.4)
9 Months Retention 95% CI for percentage	19/27 (70.4) (49.8, 86.2)	13/16 (81.3) (54.4, 96.0)
12 Months Retention 95% CI for percentage	18/27 (66.7) (46.0, 83.5)	12/16 (75.0) (47.6, 92.7)

AED=antiepileptic drug; CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: n is the number of patients with brivaracetam retention at the corresponding visit. The windows for retention from first brivaracetam dosing to the last brivaracetam administration date were ≥80 days, ≥170 days, ≥260 days, and ≥330 days, respectively, for the visits of 3/6/9/12 months. Nsub is the number of patients in the corresponding concomitant AED category.

Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.2.5, Table 6.2.6

Table 10-15: Brivaracetam retention at 3/6/9/12 months by subgroup: treatment line in adjunctive therapy (SS and PPS)

Retention	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Treatment line in adjunctive therapy: First		
3 Months Retention 95% CI for percentage	179/197 (90.9) (85.9, 94.5)	141/155 (91.0) (85.3, 95.0)
6 Months Retention 95% CI for percentage	158/197 (80.2) (73.9, 85.5)	124/155 (80.0) (72.8, 86.0)
9 Months Retention 95% CI for percentage	151/197 (76.6) (70.1, 82.4)	120/155 (77.4) (70.0, 83.7)
12 Months Retention 95% CI for percentage	147/197 (74.6) (67.9, 80.5)	117/155 (75.5) (67.9, 82.0)
Treatment line in adjunctive therapy: Second		
3 Months Retention 95% CI for percentage	125/138 (90.6) (84.4, 94.9)	95/107 (88.8) (81.2, 94.1)
6 Months Retention 95% CI for percentage	118/138 (85.5) (78.5, 90.9)	90/107 (84.1) (75.8, 90.5)
9 Months Retention 95% CI for percentage	115/138 (83.3) (76.0, 89.1)	89/107 (83.2) (74.7, 89.7)
12 Months Retention 95% CI for percentage	109/138 (79.0) (71.2, 85.5)	84/107 (78.5) (69.5, 85.9)
Treatment line in adjunctive therapy: Third		
3 Months Retention 95% CI for percentage	43/47 (91.5) (79.6, 97.6)	39/41 (95.1) (83.5, 99.4)
6 Months Retention 95% CI for percentage	41/47 (87.2) (74.3, 95.2)	37/41 (90.2) (76.9, 97.3)
9 Months Retention 95% CI for percentage	36/47 (76.6) (62.0, 87.7)	33/41 (80.5) (65.1, 91.2)
12 Months Retention 95% CI for percentage	35/47 (74.5) (59.7, 86.1)	32/41 (78.0) (62.4, 89.4)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.

Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: n is the number of patients with brivaracetam retention at the corresponding visit. The windows for retention from first brivaracetam dosing to the last brivaracetam administration date were ≥80 days, ≥170 days, ≥260 days, and ≥330 days, respectively, for the visit of 3/6/9/12 months. Nsub is the number of patients in the corresponding adjunctive treatment line category.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.2.7, Table 6.2.8

Table 10-16: Brivaracetam retention at 3/6/9/12 months by subgroup: 28-day Baseline all types POS frequency (SS and PPS)

Retention	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
28-day Baseline all types POS frequency: >0 to <1		
3 Months Retention 95% CI for percentage	97/106 (91.5) (84.5, 96.0)	72/79 (91.1) (82.6, 96.4)
6 Months Retention 95% CI for percentage	88/106 (83.0) (74.5, 89.6)	64/79 (81.0) (70.6, 89.0)
9 Months Retention 95% CI for percentage	85/106 (80.2) (71.3, 87.3)	61/79 (77.2) (66.4, 85.9)
12 Months Retention 95% CI for percentage	80/106 (75.5) (66.2, 83.3)	56/79 (70.9) (59.6, 80.6)
28-day Baseline all types POS frequency: 1 to 5		
3 Months Retention 95% CI for percentage	182/202 (90.1) (85.1, 93.8)	143/157 (91.1) (85.5, 95.0)
6 Months Retention 95% CI for percentage	170/202 (84.2) (78.4, 88.9)	133/157 (84.7) (78.1, 90.0)
9 Months Retention 95% CI for percentage	162/202 (80.2) (74.0, 85.5)	130/157 (82.8) (76.0, 88.4)
12 Months Retention 95% CI for percentage	159/202 (78.7) (72.4, 84.1)	128/157 (81.5) (74.6, 87.3)
28-day Baseline all types POS frequency: >5 to 10		
3 Months Retention 95% CI for percentage	27/30 (90.0) (73.5, 97.9)	25/26 (96.2) (80.4, 99.9)
6 Months Retention 95% CI for percentage	24/30 (80.0) (61.4, 92.3)	22/26 (84.6) (65.1, 95.6)
9 Months Retention 95% CI for percentage	22/30 (73.3) (54.1, 87.7)	20/26 (76.9) (56.4, 91.0)

Table 10-16: Brivaracetam retention at 3/6/9/12 months by subgroup: 28-day Baseline all types POS frequency (SS and PPS)

Retention	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
12 Months Retention 95% CI for percentage	21/30 (70.0) (50.6, 85.3)	19/26 (73.1) (52.2, 88.4)
28-day Baseline all types POS frequency: >10		
3 Months Retention 95% CI for percentage	38/43 (88.4) (74.9, 96.1)	32/36 (88.9) (73.9, 96.9)
6 Months Retention 95% CI for percentage	35/43 (81.4) (66.6, 91.6)	29/36 (80.6) (64.0, 91.8)
9 Months Retention 95% CI for percentage	33/43 (76.7) (61.4, 88.2)	28/36 (77.8) (60.8, 89.9)
12 Months Retention 95% CI for percentage	33/43 (76.7) (61.4, 88.2)	28/36 (77.8) (60.8, 89.9)

AED=antiepileptic drug; CI=confidence interval; POS=partial-onset seizure; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: n is the number of patients with brivaracetam retention at the corresponding visit. The windows for retention from first brivaracetam dosing to the last brivaracetam administration date were ≥80 days, ≥170 days, ≥260 days, and ≥330 days, respectively, for the visits of 3/6/9/12 months. Nsub is the number of patients in the corresponding category of Baseline POS frequency.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.2.9, Table 6.2.10

10.3.2.2 Seizure freedom at 3, 6, 9, and 12 months

Seizure freedom at 3, 6, 9, and 12 months is presented for the SS and the PPS in Table 10-17.

Table 10-17: Seizure freedom at 3/6/9/12 months (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 3 months 95% CI for percentage	115/328 (35.1) (29.9, 40.5)	89/258 (34.5) (28.7, 40.6)
Seizure freedom up to 6 months 95% CI for percentage	81/293 (27.6) (22.6, 33.1)	65/234 (27.8) (22.1, 34.0)
Seizure freedom up to 9 months 95% CI for percentage	59/266 (22.2) (17.3, 27.7)	47/214 (22.0) (16.6, 28.1)

Table 10-17: Seizure freedom at 3/6/9/12 months (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 12 months 95% CI for percentage	52/254 (20.5) (15.7, 26.0)	41/206 (19.9) (14.7, 26.0)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who completed the respective timepoint and interim timepoints with nonmissing seizure data (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit. Seizure freedom (Yes) was defined as patients with no seizures recorded prior to the visit and who had available seizure data at that and each prior visit they attended. Patients who did not have available seizure data were counted as non-seizure freedom.
Source: Table 6.3.1.1, Table 6.3.1.2

10.3.2.2.1 Subgroup analysis

Seizure freedom at 3, 6, 9, and 12 months within each subgroup is presented in Table 10-18, Table 10-19, Table 10-20, and Table 10-21.

In both the SS and the PPS, seizure freedom up to 3 and 6 months was numerically higher in subgroups of patients with 1 or 2 lifetime AEDs compared with the subgroup of patients with 3 lifetime AEDs. However, seizure freedom up to 9 and 12 months was generally comparable across the 3 subgroups in the SS and numerically lower in the subgroup with 1 lifetime AED in the PPS.

A similar trend was also observed in seizure freedom by number of treatment lines, where higher seizure freedom was observed in the subgroup with brivaracetam as first adjunctive treatment line at 3 and 6 months, while slightly higher seizure freedom at 9 and 12 months occurred in the subgroup with brivaracetam as third treatment line.

The above observations could be impacted by the lack of ability to draw conclusions from the data due to small sample sizes, which may be especially true at later visits due to patient dropouts.

Seizure freedom was higher in subgroups with <5 Baseline POS frequency over time compared with those with higher Baseline POS frequency. The highest seizure freedom was observed in the subgroup with 0 to 1 Baseline POS frequency.

Table 10-18: Seizure freedom at 3/6/9/12 months by subgroup: number of lifetime AEDs (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of lifetime AEDs: 1		
Seizure freedom up to 3 months 95% CI for percentage	36/97 (37.1) (27.5, 47.5)	27/82 (32.9) (22.9, 44.2)
Seizure freedom up to 6 months 95% CI for percentage	26/88 (29.5) (20.3, 40.2)	20/75 (26.7) (17.1, 38.1)
Seizure freedom up to 9 months 95% CI for percentage	18/83 (21.7) (13.4, 32.1)	13/70 (18.6) (10.3, 29.7)
Seizure freedom up to 12 months 95% CI for percentage	16/83 (19.3) (11.4, 29.4)	11/70 (15.7) (8.1, 26.4)
Number of lifetime AEDs: 2		
Seizure freedom up to 3 months 95% CI for percentage	54/136 (39.7) (31.4, 48.4)	42/103 (40.8) (31.2, 50.9)
Seizure freedom up to 6 months 95% CI for percentage	35/120 (29.2) (21.2, 38.2)	28/92 (30.4) (21.3, 40.9)
Seizure freedom up to 9 months 95% CI for percentage	25/108 (23.1) (15.6, 32.2)	19/84 (22.6) (14.2, 33.0)
Seizure freedom up to 12 months 95% CI for percentage	22/103 (21.4) (13.9, 30.5)	17/79 (21.5) (13.1, 32.2)
Number of lifetime AEDs: 3		
Seizure freedom up to 3 months 95% CI for percentage	20/80 (25.0) (16.0, 35.9)	17/68 (25.0) (15.3, 37.0)
Seizure freedom up to 6 months 95% CI for percentage	17/73 (23.3) (14.2, 34.6)	15/63 (23.8) (14.0, 36.2)
Seizure freedom up to 9 months 95% CI for percentage	15/65 (23.1) (13.5, 35.2)	14/58 (24.1) (13.9, 37.2)
Seizure freedom up to 12 months 95% CI for percentage	13/60 (21.7) (12.1, 34.2)	12/55 (21.8) (11.8, 35.0)

AED=antiepileptic drug; CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who completed the respective timepoint and interim timepoints with nonmissing seizure data (Nsub).

Note: n is the number of patients with seizure freedom at the corresponding visit. Seizure freedom (Yes) was defined as patients with no seizures recorded prior to the visit and who had available seizure data at that and each prior visit they attended. Patients who did not have available seizure data were counted as non-seizure freedom.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Lifetime AEDs were defined as a sum of the prior AEDs and concomitant AEDs medications at brivaracetam initiation. An AED was counted as a lifetime AED if it was used for the treatment of seizures for at least 7 consecutive days (1 week) any time before brivaracetam initiation (excluding benzodiazepines or other rescue medications used short term per physician discretion).
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.1.3, Table 6.3.1.4

Table 10-19: Seizure freedom at 3/6/9/12 months by subgroup: number of concomitant AEDs (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of concomitant AEDs: 1		
Seizure freedom up to 3 months 95% CI for percentage	74/192 (38.5) (31.6, 45.8)	56/159 (35.2) (27.8, 43.2)
Seizure freedom up to 6 months 95% CI for percentage	49/173 (28.3) (21.7, 35.7)	38/146 (26.0) (19.1, 33.9)
Seizure freedom up to 9 months 95% CI for percentage	37/161 (23.0) (16.7, 30.3)	28/137 (20.4) (14.0, 28.2)
Seizure freedom up to 12 months 95% CI for percentage	33/157 (21.0) (14.9, 28.2)	24/133 (18.0) (11.9, 25.6)
Number of concomitant AEDs: 2		
Seizure freedom up to 3 months 95% CI for percentage	36/110 (32.7) (24.1, 42.3)	29/82 (35.4) (25.1, 46.7)
Seizure freedom up to 6 months 95% CI for percentage	27/97 (27.8) (19.2, 37.9)	23/73 (31.5) (21.1, 43.4)
Seizure freedom up to 9 months 95% CI for percentage	19/85 (22.4) (14.0, 32.7)	16/64 (25.0) (15.0, 37.4)
Seizure freedom up to 12 months 95% CI for percentage	17/80 (21.3) (12.9, 31.8)	15/61 (24.6) (14.5, 37.3)
Number of concomitant AEDs: 3		
Seizure freedom up to 3 months 95% CI for percentage	5/21 (23.8) (8.2, 47.2)	4/15 (26.7) (7.8, 55.1)
Seizure freedom up to 6 months 95% CI for percentage	5/18 (27.8) (9.7, 53.5)	4/13 (30.8) (9.1, 61.4)

Table 10-19: Seizure freedom at 3/6/9/12 months by subgroup: number of concomitant AEDs (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 9 months 95% CI for percentage	3/15 (20.0) (4.3, 48.1)	3/11 (27.3) (6.0, 61.0)
Seizure freedom up to 12 months 95% CI for percentage	2/14 (14.3) (1.8, 42.8)	2/10 (20.0) (2.5, 55.6)

AED=antiepileptic drug; CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who completed the respective timepoint and interim timepoints with nonmissing seizure data (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit. Seizure freedom (Yes) was defined as patients with no seizures recorded prior to the visit and who had available seizure data at that and each prior visit they attended. Patients who did not have available seizure data were counted as non-seizure freedom.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.1.5, Table 6.3.1.6

Table 10-20: Seizure freedom at 3/6/9/12 months by subgroup: treatment line in adjunctive therapy (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Treatment line in adjunctive therapy: First		
Seizure freedom up to 3 months 95% CI for percentage	65/165 (39.4) (31.9, 47.3)	48/129 (37.2) (28.9, 46.2)
Seizure freedom up to 6 months 95% CI for percentage	45/145 (31.0) (23.6, 39.2)	34/115 (29.6) (21.4, 38.8)
Seizure freedom up to 9 months 95% CI for percentage	32/133 (24.1) (17.1, 32.2)	23/106 (21.7) (14.3, 30.8)
Seizure freedom up to 12 months 95% CI for percentage	29/128 (22.7) (15.7, 30.9)	20/102 (19.6) (12.4, 28.6)
Treatment line in adjunctive therapy: Second		
Seizure freedom up to 3 months 95% CI for percentage	37/116 (31.9) (23.6, 41.2)	29/89 (32.6) (23.0, 43.3)
Seizure freedom up to 6 months 95% CI for percentage	25/104 (24.0) (16.2, 33.4)	21/82 (25.6) (16.6, 36.4)

Table 10-20: Seizure freedom at 3/6/9/12 months by subgroup: treatment line in adjunctive therapy (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 9 months 95% CI for percentage	18/94 (19.1) (11.8, 28.6)	15/75 (20.0) (11.6, 30.8)
Seizure freedom up to 12 months 95% CI for percentage	15/92 (16.3) (9.4, 25.5)	13/73 (17.8) (9.8, 28.5)
Treatment line in adjunctive therapy: Third		
Seizure freedom up to 3 months 95% CI for percentage	12/43 (27.9) (15.3, 43.7)	12/39 (30.8) (17.0, 47.6)
Seizure freedom up to 6 months 95% CI for percentage	10/40 (25.0) (12.7, 41.2)	10/36 (27.8) (14.2, 45.2)
Seizure freedom up to 9 months 95% CI for percentage	9/35 (25.7) (12.5, 43.3)	9/32 (28.1) (13.7, 46.7)
Seizure freedom up to 12 months 95% CI for percentage	8/31 (25.8) (11.9, 44.6)	8/30 (26.7) (12.3, 45.9)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who completed the respective timepoint and interim timepoints with nonmissing seizure data (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit. Seizure freedom (Yes) was defined as patients with no seizures recorded prior to the visit and who had available seizure data at that and each prior visit they attended. Patients who did not have available seizure data were counted as non-seizure freedom.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.1.7, Table 6.3.1.8

Table 10-21: Seizure freedom at 3/6/9/12 months by subgroup: 28-day Baseline all types POS frequency (SS and PPS)

Seizure Freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
28-day Baseline all types POS frequency: >0 to <1		
Seizure freedom up to 3 months 95% CI for percentage	51/92 (55.4) (44.7, 65.8)	38/68 (55.9) (43.3, 67.9)
Seizure freedom up to 6 months 95% CI for percentage	35/82 (42.7) (31.8, 54.1)	27/62 (43.5) (31.0, 56.7)

Table 10-21: Seizure freedom at 3/6/9/12 months by subgroup: 28-day Baseline all types POS frequency (SS and PPS)

Seizure Freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 9 months 95% CI for percentage	23/72 (31.9) (21.4, 44.0)	18/54 (33.3) (21.1, 47.5)
Seizure freedom up to 12 months 95% CI for percentage	20/68 (29.4) (19.0, 41.7)	15/50 (30.0) (17.9, 44.6)
28-day Baseline all types POS frequency: 1 to 5		
Seizure freedom up to 3 months 95% CI for percentage	55/172 (32.0) (25.1, 39.5)	45/138 (32.6) (24.9, 41.1)
Seizure freedom up to 6 months 95% CI for percentage	41/156 (26.3) (19.6, 33.9)	33/124 (26.6) (19.1, 35.3)
Seizure freedom up to 9 months 95% CI for percentage	32/145 (22.1) (15.6, 29.7)	25/117 (21.4) (14.3, 29.9)
Seizure freedom up to 12 months 95% CI for percentage	28/139 (20.1) (13.8, 27.8)	22/114 (19.3) (12.5, 27.7)
28-day Baseline all types POS frequency: >5 to 10		
Seizure freedom up to 3 months 95% CI for percentage	3/24 (12.5) (2.7, 32.4)	3/22 (13.6) (2.9, 34.9)
Seizure freedom up to 6 months 95% CI for percentage	2/22 (9.1) (1.1, 29.2)	2/21 (9.5) (1.2, 30.4)
Seizure freedom up to 9 months 95% CI for percentage	1/19 (5.3) (0.1, 26.0)	1/18 (5.6) (0.1, 27.3)
Seizure freedom up to 12 months 95% CI for percentage	1/18 (5.6) (0.1, 27.3)	1/17 (5.9) (0.1, 28.7)
28-day Baseline all types POS frequency: >10		
Seizure freedom up to 3 months 95% CI for percentage	4/35 (11.4) (3.2, 26.7)	3/29 (10.3) (2.2, 27.4)
Seizure freedom up to 6 months 95% CI for percentage	3/30 (10.0) (2.1, 26.5)	3/26 (11.5) (2.4, 30.2)
Seizure freedom up to 9 months 95% CI for percentage	3/28 (10.7) (2.3, 28.2)	3/24 (12.5) (2.7, 32.4)
Seizure freedom up to 12 months 95% CI for percentage	3/28 (10.7) (2.3, 28.2)	3/24 (12.5) (2.7, 32.4)

CI=confidence interval; POS=partial-onset seizure; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who completed the respective timepoint and interim timepoints with nonmissing seizure data (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit. Seizure freedom (Yes) was defined as patients with no seizures recorded prior to the visit and who had available seizure data at that and each prior visit they attended. Patients who did not have available seizure data were counted as non-seizure freedom.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.1.9, Table 6.3.1.10

10.3.2.3 Sensitivity analysis: seizure freedom at 3, 6, 9, and 12 months

A sensitivity analysis was performed following a less conservative approach for seizure freedom calculation than the primary seizure freedom analysis: missing seizure counts were included in the calculation of seizure freedom and were considered seizure free, irrespective of whether other types of data were present at the same visit (see Section 9.9.5).

Seizure freedom at 3, 6, 9, and 12 months per the sensitivity analysis is presented for the SS and the PPS in Table 10-22. The sensitivity analysis was supportive of the main effectiveness analysis and did not lead to different conclusions about seizure freedom (Section 10.3.2.2).

Table 10-22: Sensitivity analysis of seizure freedom at 3/6/9/12 months (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 3 months 95% CI for percentage	135/348 (38.8) (33.6, 44.1)	103/272 (37.9) (32.1, 43.9)
Seizure freedom up to 6 months 95% CI for percentage	98/324 (30.2) (25.3, 35.6)	76/254 (29.9) (24.4, 36.0)
Seizure freedom up to 9 months 95% CI for percentage	76/312 (24.4) (19.7, 29.5)	60/246 (24.4) (19.2, 30.3)
Seizure freedom up to 12 months 95% CI for percentage	66/296 (22.3) (17.7, 27.5)	52/236 (22.0) (16.9, 27.9)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who were still in the study by the corresponding timepoint (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit.
Note: For the sensitivity analysis, missing seizure counts were considered to be seizure free, irrespective of whether seizure data was missing.
Note: Manual medical review confirmed patients' exclusion or inclusion in the PPS.
Source: Table 6.3.2.1, Table 6.3.2.2

10.3.2.3.1 Sensitivity analysis by Subgroup

Seizure freedom at 3, 6, 9, and 12 months within each subgroup per the sensitivity analysis is presented in Table 10-23, Table 10-24, Table 10-25, and Table 10-26. The outcomes are comparable and show no meaningful differences with the original analysis.

Table 10-23: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: lifetime AEDs (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of lifetime AEDs: 1		
Seizure freedom up to 3 months 95% CI for percentage	40/101 (39.6) (30.0, 49.8)	31/86 (36.0) (26.0, 47.1)
Seizure freedom up to 6 months 95% CI for percentage	30/95 (31.6) (22.4, 41.9)	23/81 (28.4) (18.9, 39.5)
Seizure freedom up to 9 months 95% CI for percentage	22/94 (23.4) (15.3, 33.3)	16/80 (20.0) (11.9, 30.4)
Seizure freedom up to 12 months 95% CI for percentage	19/92 (20.7) (12.9, 30.4)	13/78 (16.7) (9.2, 26.8)
Number of lifetime AEDs: 2		
Seizure freedom up to 3 months 95% CI for percentage	67/149 (45.0) (36.8, 53.3)	51/112 (45.5) (36.1, 55.2)
Seizure freedom up to 6 months 95% CI for percentage	45/137 (32.8) (25.1, 41.4)	35/103 (34.0) (24.9, 44.0)
Seizure freedom up to 9 months 95% CI for percentage	34/132 (25.8) (18.5, 34.1)	27/100 (27.0) (18.6, 36.8)
Seizure freedom up to 12 months 95% CI for percentage	30/126 (23.8) (16.7, 32.2)	24/95 (25.3) (16.9, 35.2)
Number of lifetime AEDs: 3		
Seizure freedom up to 3 months 95% CI for percentage	21/81 (25.9) (16.8, 36.9)	18/69 (26.1) (16.3, 38.1)
Seizure freedom up to 6 months 95% CI for percentage	19/77 (24.7) (15.6, 35.8)	16/66 (24.2) (14.5, 36.4)
Seizure freedom up to 9 months 95% CI for percentage	17/71 (23.9) (14.6, 35.5)	15/62 (24.2) (14.2, 36.7)
Seizure freedom up to 12 months 95% CI for percentage	14/65 (21.5) (12.3, 33.5)	13/59 (22.0) (12.3, 34.7)

AED=antiepileptic drug; CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who were still in the study by the corresponding timepoint (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit.
Note: For this sensitivity analysis, missing seizure counts were considered to be seizure free, irrespective of whether seizure data were missing.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes. In addition, the subgroup category of patients with >3 lifetime AEDs is not presented due to small sample sizes (≤11 patients in the SS; 0 patients in the PPS).
Source: Table 6.3.2.3, Table 6.3.2.4

Table 10-24: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: concomitant AEDs (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Number of concomitant AEDs: 1		
Seizure freedom up to 3 months 95% CI for percentage	87/205 (42.4) (35.6, 49.5)	66/169 (39.1) (31.7, 46.8)
Seizure freedom up to 6 months 95% CI for percentage	60/192 (31.3) (24.8, 38.3)	44/158 (27.8) (21.0, 35.5)
Seizure freedom up to 9 months 95% CI for percentage	45/185 (24.3) (18.3, 31.2)	32/154 (20.8) (14.7, 28.0)
Seizure freedom up to 12 months 95% CI for percentage	39/178 (21.9) (16.1, 28.7)	27/148 (18.2) (12.4, 25.4)
Number of concomitant AEDs: 2		
Seizure freedom up to 3 months 95% CI for percentage	42/116 (36.2) (27.5, 45.6)	33/86 (38.4) (28.1, 49.5)
Seizure freedom up to 6 months 95% CI for percentage	33/107 (30.8) (22.3, 40.5)	28/80 (35.0) (24.7, 46.5)
Seizure freedom up to 9 months 95% CI for percentage	27/103 (26.2) (18.0, 35.8)	24/77 (31.2) (21.1, 42.7)
Seizure freedom up to 12 months 95% CI for percentage	24/97 (24.7) (16.5, 34.5)	22/74 (29.7) (19.7, 41.5)
Number of concomitant AEDs: 3		
Seizure freedom up to 3 months 95% CI for percentage	6/22 (27.3) (10.7, 50.2)	4/15 (26.7) (7.8, 55.1)
Seizure freedom up to 6 months 95% CI for percentage	5/20 (25.0) (8.7, 49.1)	4/14 (28.6) (8.4, 58.1)

Table 10-24: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: concomitant AEDs (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 9 months 95% CI for percentage	4/19 (21.1) (6.1, 45.6)	4/13 (30.8) (9.1, 61.4)
Seizure freedom up to 12 months 95% CI for percentage	3/18 (16.7) (3.6, 41.4)	3/12 (25.0) (5.5, 57.2)

AED=antiepileptic drug; CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who were still in the study by the corresponding timepoint (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit.
Note: For this sensitivity analysis, missing seizure counts were considered to be seizure free, irrespective of whether seizure data were missing.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.2.5, Table 6.3.2.6

Table 10-25: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: treatment line in adjunctive therapy (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Treatment line in adjunctive therapy: First		
Seizure freedom up to 3 months 95% CI for percentage	75/175 (42.9) (35.4, 50.5)	57/138 (41.3) (33.0, 50.0)
Seizure freedom up to 6 months 95% CI for percentage	56/161 (34.8) (27.5, 42.7)	41/126 (32.5) (24.5, 41.5)
Seizure freedom up to 9 months 95% CI for percentage	42/155 (27.1) (20.3, 34.8)	31/123 (25.2) (17.8, 33.8)
Seizure freedom up to 12 months 95% CI for percentage	36/147 (24.5) (17.8, 32.3)	26/117 (22.2) (15.1, 30.8)
Treatment line in adjunctive therapy: Second		
Seizure freedom up to 3 months 95% CI for percentage	46/125 (36.8) (28.4, 45.9)	34/94 (36.2) (26.5, 46.7)
Seizure freedom up to 6 months 95% CI for percentage	31/117 (26.5) (18.8, 35.5)	25/90 (27.8) (18.9, 38.2)

Table 10-25: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: treatment line in adjunctive therapy (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 9 months 95% CI for percentage	25/114 (21.9) (14.7, 30.6)	20/88 (22.7) (14.5, 32.9)
Seizure freedom up to 12 months 95% CI for percentage	22/111 (19.8) (12.9, 28.5)	18/86 (20.9) (12.9, 31.0)
Treatment line in adjunctive therapy: Third		
Seizure freedom up to 3 months 95% CI for percentage	12/43 (27.9) (15.3, 43.7)	12/39 (30.8) (17.0, 47.6)
Seizure freedom up to 6 months 95% CI for percentage	10/41 (24.4) (12.4, 40.3)	10/37 (27.0) (13.8, 44.1)
Seizure freedom up to 9 months 95% CI for percentage	9/38 (23.7) (11.4, 40.2)	9/34 (26.5) (12.9, 44.4)
Seizure freedom up to 12 months 95% CI for percentage	8/34 (23.5) (10.7, 41.2)	8/32 (25.0) (11.5, 43.4)

CI=confidence interval; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who were still in the study by the corresponding timepoint (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit.
Note: For this sensitivity analysis, missing seizure counts were considered to be seizure free, irrespective of whether seizure data were missing.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.2.7, Table 6.3.2.8

Table 10-26: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: 28-day Baseline all types POS frequency (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
28-day Baseline all types POS frequency: >0-<1		
Seizure freedom up to 3 months 95% CI for percentage	55/96 (57.3) (46.8, 67.3)	40/70 (57.1) (44.7, 68.9)
Seizure freedom up to 6 months 95% CI for percentage	39/89 (43.8) (33.3, 54.7)	29/65 (44.6) (32.3, 57.5)

Table 10-26: Sensitivity analysis of seizure freedom at 3/6/9/12 months by subgroup: 28-day Baseline all types POS frequency (SS and PPS)

Seizure freedom	All patients (SS) N=392 n/Nsub (%)	All patients (PPS) N=304 n/Nsub (%)
Seizure freedom up to 9 months 95% CI for percentage	28/87 (32.2) (22.6, 43.1)	22/63 (34.9) (23.3, 48.0)
Seizure freedom up to 12 months 95% CI for percentage	25/82 (30.5) (20.8, 41.6)	19/58 (32.8) (21.0, 46.3)
28-day Baseline all types POS frequency: 1-5		
Seizure freedom up to 3 months 95% CI for percentage	64/181 (35.4) (28.4, 42.8)	50/143 (35.0) (27.2, 43.4)
Seizure freedom up to 6 months 95% CI for percentage	48/169 (28.4) (21.7, 35.8)	38/133 (28.6) (21.1, 37.0)
Seizure freedom up to 9 months 95% CI for percentage	39/164 (23.8) (17.5, 31.0)	31/131 (23.7) (16.7, 31.9)
Seizure freedom up to 12 months 95% CI for percentage	34/156 (21.8) (15.6, 29.1)	27/127 (21.3) (14.5, 29.4)
28-day Baseline all types POS frequency: >5-10		
Seizure freedom up to 3 months 95% CI for percentage	4/25 (16.0) (4.5, 36.1)	4/23 (17.4) (5.0, 38.8)
Seizure freedom up to 6 months 95% CI for percentage	3/24 (12.5) (2.7, 32.4)	3/22 (13.6) (2.9, 34.9)
Seizure freedom up to 9 months 95% CI for percentage	2/22 (9.1) (1.1, 29.2)	2/20 (10.0) (1.2, 31.7)
Seizure freedom up to 12 months 95% CI for percentage	1/21 (4.8) (0.1, 23.8)	1/19 (5.3) (0.1, 26.0)
28-day Baseline all types POS frequency: >10		
Seizure freedom up to 3 months 95% CI for percentage	7/38 (18.4) (7.7, 34.3)	6/32 (18.8) (7.2, 36.4)
Seizure freedom up to 6 months 95% CI for percentage	4/35 (11.4) (3.2, 26.7)	3/30 (10.0) (2.1, 26.5)
Seizure freedom up to 9 months 95% CI for percentage	4/33 (12.1) (3.4, 28.2)	3/28 (10.7) (2.3, 28.2)
Seizure freedom up to 12 months 95% CI for percentage	4/33 (12.1) (3.4, 28.2)	3/28 (10.7) (2.3, 28.2)

CI=confidence interval; POS=partial-onset seizure; PPS=Per Protocol Set; SS=Safety Set.
Note: CIs were calculated using 2-sided exact (Clopper-Pearson) method.
Note: Percentage is based on the denominator for number of patients who were still in the study by the corresponding timepoint (Nsub).
Note: n is the number of patients with seizure freedom at the corresponding visit.
Note: For this sensitivity analysis, missing seizure counts were considered to be seizure free, irrespective of whether seizure data were missing.
Note: Subgroups with ≤10 patients are not presented as no meaningful interpretations were possible due to small sample sizes.
Source: Table 6.3.2.9, Table 6.3.2.10

10.3.2.4 POS frequency at Baseline, 3, 6, 9, and 12 months

All types POS frequency was recorded for the SS and the PPS and is presented for each visit in Table 10-27. Median POS frequency decreased at all timepoints from Visit 1 (Baseline) to Visit 5 (Month 12).

Table 10-27: All types POS frequency (SS and PPS)

Visit	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Visit 1 (Baseline)	n	385	298
	Mean (SD)	6.19 (21.61)	6.95 (24.29)
	Median (Q1, Q3)	1.67 (0.67, 4.00)	2.00 (0.67, 4.00)
	IQR	3.33	3.33
	Min, Max	0.0, 300.0	0.3, 300.0
Visit 2 (Month 3)	n	326	257
	Mean (SD)	4.37 (24.84)	4.99 (27.84)
	Median (Q1, Q3)	0.57 (0.00, 1.85)	0.60 (0.00, 2.07)
	IQR	1.85	2.07
	Min, Max	0.0, 335.4	0.0, 335.4
Visit 3 (Month 6)	n	303	241
	Mean (SD)	3.06 (15.14)	3.41 (16.84)
	Median (Q1, Q3)	0.31 (0.00, 1.83)	0.32 (0.00, 1.83)
	IQR	1.83	1.83
	Min, Max	0.0, 235.5	0.0, 235.5
Visit 4 (Month 9)	n	284	224
	Mean (SD)	4.72 (30.48)	5.60 (34.25)
	Median (Q1, Q3)	0.30 (0.00, 1.37)	0.30 (0.00, 1.46)
	IQR	1.37	1.46
	Min, Max	0.0, 370.9	0.0, 370.9

Table 10-27: All types POS frequency (SS and PPS)

Visit	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Visit 5 (Month 12)	n	294	234
	Mean (SD)	3.20 (16.56)	3.57 (18.42)
	Median (Q1, Q3)	0.00 (0.00, 1.31)	0.00 (0.00, 1.22)
	IQR	1.31	1.22
	Min, Max	0.0, 259.8	0.0, 259.8

IQR=interquartile range; Max=maximum; Min=minimum; POS=partial-onset seizure; PPS=Per Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set.
Note: Seizure frequency summarized in this table is 28-day adjusted seizure frequency.
Source: Table 6.4.1, Table 6.4.2

10.3.2.5 Change in POS frequency from Baseline to 3, 6, 9, and 12 months

10.3.2.5.1 Absolute reduction

Absolute reduction in all types POS frequency was measured as described in Section 9.4.2.1.

The absolute reduction in all types POS frequency from Baseline is presented for the SS and the PPS in Table 10-28. The median absolute reduction from Baseline was positive at all timepoints and consistent over time (0.71 at Visit 2 [Month 3], 1.00 at Visit 3 [Month 6], Visit 4 [Month 9], and Visit 5 [Month 12] for the SS). Similar absolute reductions were observed at all visits in the SS and the PPS.

Table 10-28: Absolute reduction in all types POS frequency from Baseline (SS and PPS)

Visit	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Visit 2 (Month 3)	n	326	257
	Mean (SD)	1.77 (20.62)	1.87 (22.98)
	Median (Q1, Q3)	0.71 (0.12, 2.06)	0.78 (0.26, 2.62)
	IQR	1.94	2.36
	Min, Max	-305.4, 142.7	-305.4, 142.7
Visit 3 (Month 6)	n	302	240
	Mean (SD)	2.94 (10.95)	3.38 (11.82)
	Median (Q1, Q3)	1.00 (0.33, 2.55)	1.00 (0.33, 3.02)
	IQR	2.22	2.69
	Min, Max	-29.8, 127.5	-29.8, 127.5
Visit 4 (Month 9)	n	283	223

Table 10-28: Absolute reduction in all types POS frequency from Baseline (SS and PPS)

Visit	Statistic	All patients (SS) N=392	All patients (PPS) N=304
	Mean (SD)	1.09 (23.31)	0.98 (26.11)
	Median (Q1, Q3)	1.00 (0.33, 2.67)	1.00 (0.33, 3.00)
	IQR	2.33	2.67
	Min, Max	-340.9, 162.5	-340.9, 162.5
Visit 5 (Month 12)	n	292	232
	Mean (SD)	2.95 (10.85)	3.32 (11.76)
	Median (Q1, Q3)	1.00 (0.33, 2.88)	1.28 (0.33, 3.22)
	IQR	2.54	2.89
	Min, Max	-26.3, 140.8	-26.3, 140.8

IQR=interquartile range; Max=maximum; Min=minimum; POS=partial-onset seizure; PPS=Per Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set.
Note: Absolute reduction in all types POS frequency defined as: 28-day Baseline seizure frequency – 28-day post Baseline seizure frequency. A positive value means a reduction in seizure frequency.
Source: Table 6.5.1, Table 6.5.2

10.3.2.5.2 Percent reduction

Percent reduction in all types POS frequency was measured as described in Section 9.4.2.1.

The percent reduction in all types POS frequency from Baseline is presented for the SS and the PPS in Table 10-29. The median percent reduction from Baseline was positive at all timepoints (68.60% at Visit 2 [Month 3], 81.33% at Visit 3 [Month 6], 82.50% at Visit 4 [Month 9] for the SS) and was 100.00% at Visit 5 (Month 12) in the SS and the PPS. Similar percent reductions were observed at all visits in the SS and the PPS.

Table 10-29: Percent reduction in all types POS frequency from Baseline (SS and PPS)

Visit	Statistic	All patients (SS) N=392	All patients (PPS) N=304
Visit 2 (Month 3)	n	323	257
	Mean (SD)	34.81 (120.58)	39.17 (102.75)
	Median (Q1, Q3)	68.60 (11.58, 100.00)	69.57 (12.50, 100.00)
	IQR	88.42	87.50
	Min, Max	-1018.1, 100.0	-1018.1, 100.0
Visit 3 (Month 6)	n	301	240

Table 10-29: Percent reduction in all types POS frequency from Baseline (SS and PPS)

Visit	Statistic	All patients (SS) N=392	All patients (PPS) N=304
	Mean (SD)	35.85 (135.65)	42.54 (115.68)
	Median (Q1, Q3)	81.33 (31.52, 100.0)	81.58 (38.39, 100.0)
	IQR	68.48	61.61
	Min, Max	-1020.0, 100.0	-695.8, 100.0
Visit 4 (Month 9)	n	281	223
	Mean (SD)	36.78 (142.52)	42.04 (125.77)
	Median (Q1, Q3)	82.50 (31.52, 100.0)	83.53 (33.96, 100.0)
	IQR	68.48	66.04
	Min, Max	-1175.9, 100.0	-1136.2, 100.0
Visit 5 (Month 12)	n	292	232
	Mean (SD)	44.84 (134.11)	52.19 (125.31)
	Median (Q1, Q3)	100.00 (50.27, 100.00)	100.00 (54.35, 100.00)
	IQR	49.73	45.65
	Min, Max	-1127.0, 100.0	-1127.0, 100.0

IQR=interquartile range; Max=maximum; Min=minimum; POS=partial-onset seizure; PPS=Per Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set.
Note: Positive values of percent reduction means a reduction in seizure frequency.
Source: Table 6.5.3, Table 6.5.4

10.3.2.5.3 Responders: ≥50% seizure reduction

The number and percentage of patients with ≥50% reduction in all types POS frequency from Baseline at each respective timepoint are presented in Table 10-30. The percentage of patients achieving ≥50% seizure reduction increased over time (56.0% at Visit 2 [Month 3], 68.1% at Visit 3 [Month 6], 68.7% at Visit 4 [Month 9] in the SS) with the highest seizure reduction observed at Visit 5 (Month 12) with 75.7% (in the SS). This trend was similar in the PPS.

Table 10-30: Frequency of ≥50% responders for all types POS (SS and PPS)

Visit	Statistic	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Visit 2 (Month 3)	n	323	257
	Yes	181 (56.0)	144 (56.0)
	No	142 (44.0)	113 (44.0)

Table 10-30: Frequency of ≥50% responders for all types POS (SS and PPS)

Visit	Statistic	All patients (SS) N=392 n (%)	All patients (PPS) N=304 n (%)
Visit 3 (Month 6)	n	301	240
	Yes	205 (68.1)	167 (69.6)
	No	96 (31.9)	73 (30.4)
Visit 4 (Month 9)	n	281	223
	Yes	193 (68.7)	152 (68.2)
	No	88 (31.3)	71 (31.8)
Visit 5 (Month 12)	n	292	232
	Yes	221 (75.7)	180 (77.6)
	No	71 (24.3)	52 (22.4)

POS=partial-onset seizure; PPS=Per Protocol Set; SS=Safety Set.
Note: Patients with ≥50% reduction in all types POS frequency were defined as responder = "Yes" or responder = "No" otherwise.
Note: Percentage was based on the denominator for number of patients who completed the respective timepoint with nonmissing data.
Source: Table 6.6.1, Table 6.6.2

10.3.2.6 Discontinuation of brivaracetam due to lack of effectiveness

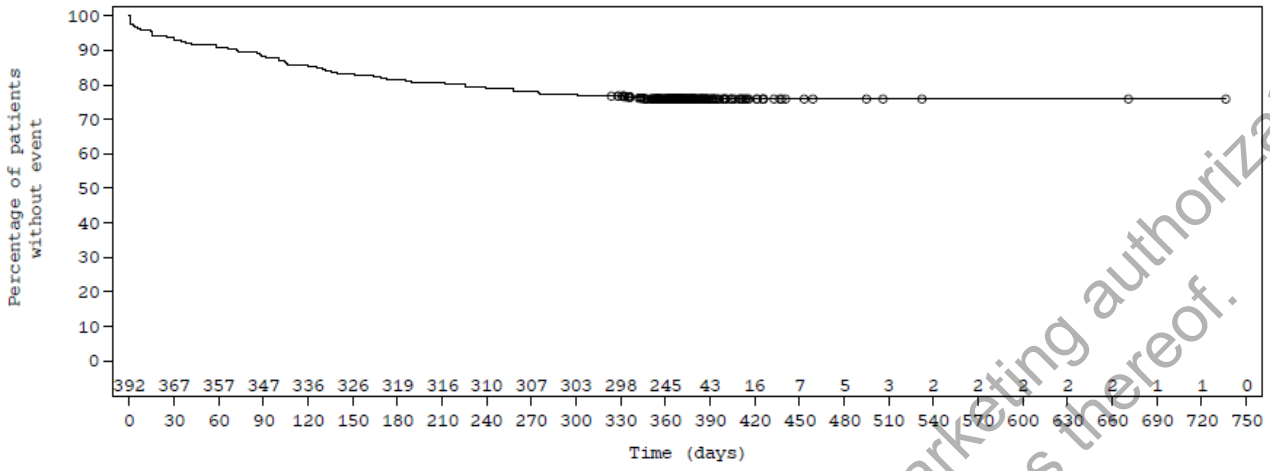
Among the SS, 17 (4.3%) patients discontinued brivaracetam due to lack of efficacy (Table 6.7.1). Among the PPS, 12 (3.9%) patients discontinued brivaracetam due to lack of efficacy (Table 6.7.2).

10.3.2.7 Time to discontinuation of brivaracetam treatment

A Kaplan-Meier analysis of time to discontinuation of brivaracetam is presented in Table 6.8.1 for the SS and in Table 6.8.2 for the PPS. Among the SS, 94 (24.0%) patients discontinued brivaracetam, and among the PPS, 67 (22.0%) patients discontinued brivaracetam.

A survival curve depicting Kaplan-Meier estimates of time to discontinuation of brivaracetam is presented for the SS in Figure 10-1 and for the PPS in Figure 10-2. Overall, the figure reflects a low number of premature discontinuations (24%), and a group of discontinuations appears after approximately 360 days which corresponds with the 12-month follow up period.

Figure 10-1: Kaplan-Meier estimation for time to discontinuation of brivaracetam (SS)



eCRF=electronic Case Report Form; SS=Safety Set.

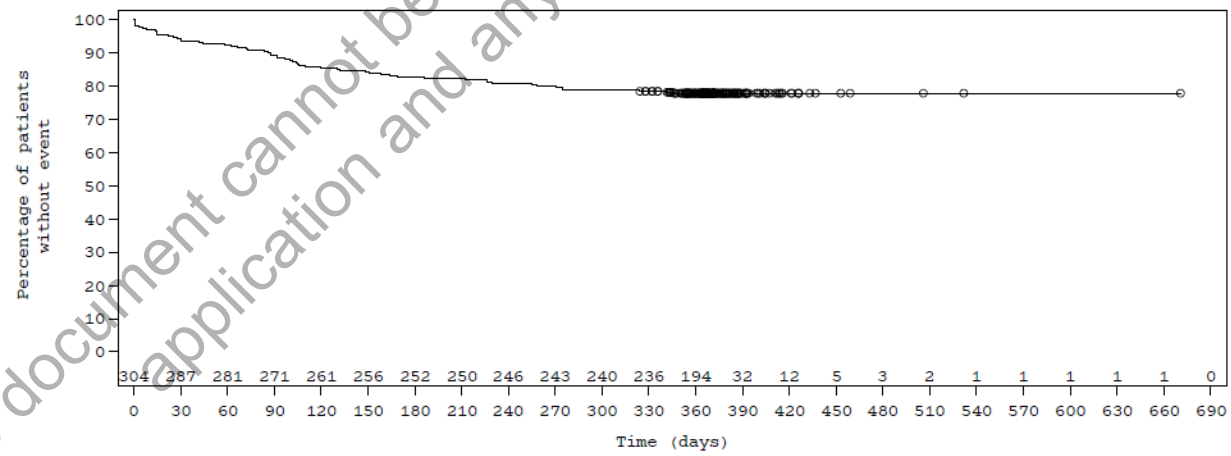
Note: Time to discontinuation of brivaracetam was calculated as: Date of last administration of brivaracetam while in the study (Study Termination eCRF page) - date of first brivaracetam administration (First Dose of Medication Received During Reference Period eCRF page) + 1. A patient was considered to be having an event if the patient discontinued brivaracetam and the Study Termination eCRF page was completed (Patient status at study termination = Dropout). Patients with continuation of brivaracetam or with missing dates of last administration of brivaracetam when the patient discontinued brivaracetam were both considered to be not having an event and were censored. The censored date was the last available date, which included the date of last administration of brivaracetam and the date of last visit.

Note: The numbers inside the plot represent the number of patients at risk.

Note: The symbols represent censored patients.

Source: Figure 1.1

Figure 10-2: Kaplan-Meier estimation for time to discontinuation of brivaracetam (PPS)



eCRF=electronic Case Report Form; PPS=Per Protocol Set.

Note: Time to discontinuation of brivaracetam was calculated as: Date of last administration of brivaracetam while in the study (Study Termination eCRF page) - date of first brivaracetam administration (First Dose of Medication Received During Reference Period eCRF page) + 1. A patient was considered to be having an event if the patient discontinued brivaracetam and the Study Termination eCRF page was completed (Patient status at study

termination = Dropout). Patients with continuation of brivaracetam or with missing dates of last administration of brivaracetam when the patient discontinued brivaracetam were both considered to be not having an event and were censored. The censored date was the last available date, which included the date of last administration of brivaracetam and the date of last visit.
Note: The numbers inside the plot represent the number of patients at risk.
Note: The symbols represent censored patients.
Source: Figure 1.2

10.3.3 Other effectiveness variables

10.3.3.1 Self-reported seizure frequency

Self-reported seizure frequency data for patients who used the Helpilepsy application are presented for the SS (n=134) in Table 7.1.1 and for the PPS (n=90) in Table 7.1.2. The number of all types of seizures, POS, partial evolve to secondary generalized, and generalized seizures are presented in the tables. The median number of all types of seizures was 0.0 at all timepoints. The corresponding means for these timepoints were >0 suggesting some skewing of the data due to large numbers.

10.3.3.2 Time to first seizure after first dose of brivaracetam

Among the SS, the median time to first seizure in patients using Helpilepsy was 82.0 days (Table 6.9.1). Among the PPS, the median time to first seizure in patients using Helpilepsy was 143.0 days (Table 6.9.2). Survival curves depicting Kaplan-Meier estimates of time to first seizure for patients using Helpilepsy are available in Figure 2.1 for the SS and Figure 2.2 for the PPS. The longer time to first seizure evidenced in the PPS could be interpreted as patients adhering to treatment recommended per SmPC showed better effectiveness outcomes; however, as this is a subset of patients (PPS set of Helpilepsy users) caution should be used for interpretation.

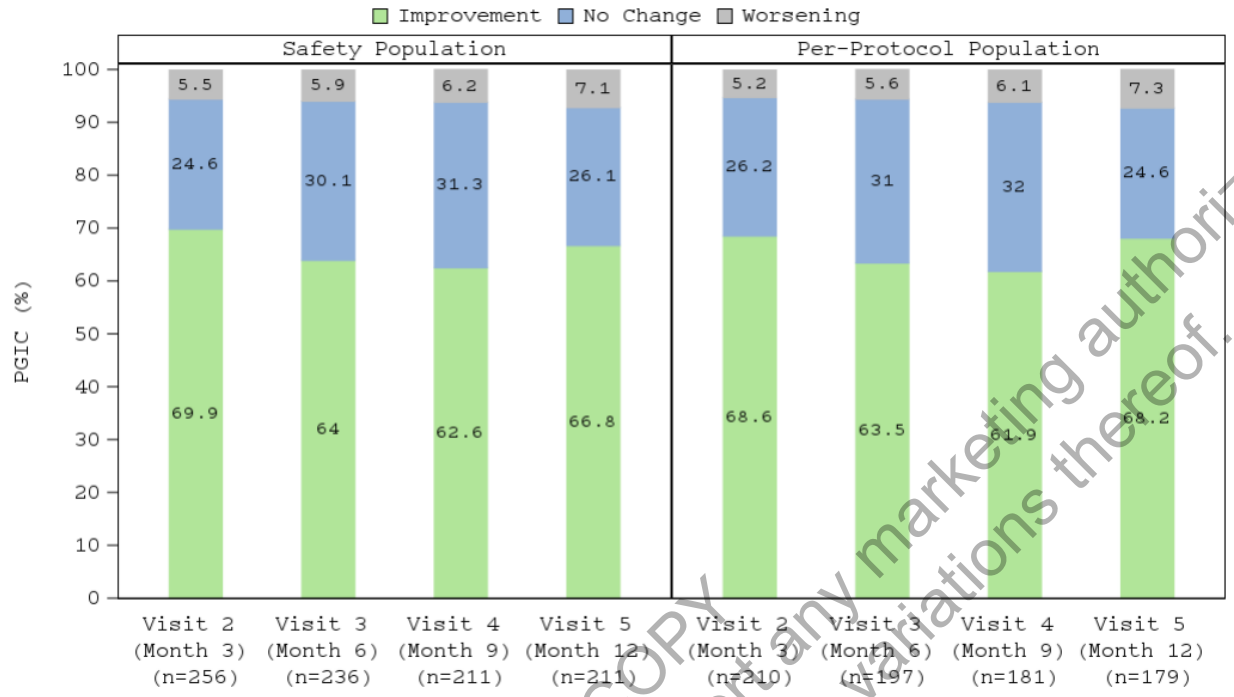
10.3.4 Health outcome variables

10.3.4.1 PGIC and CGIC

PGIC

The PGIC at each visit assessed how the patient felt over the past 4 weeks compared with before entering the study. Improvement in clinical condition was stable over time during the observational period of the study (Figure 10-3).

Figure 10-3: PGIC from Baseline by Visit (SS and PPS)



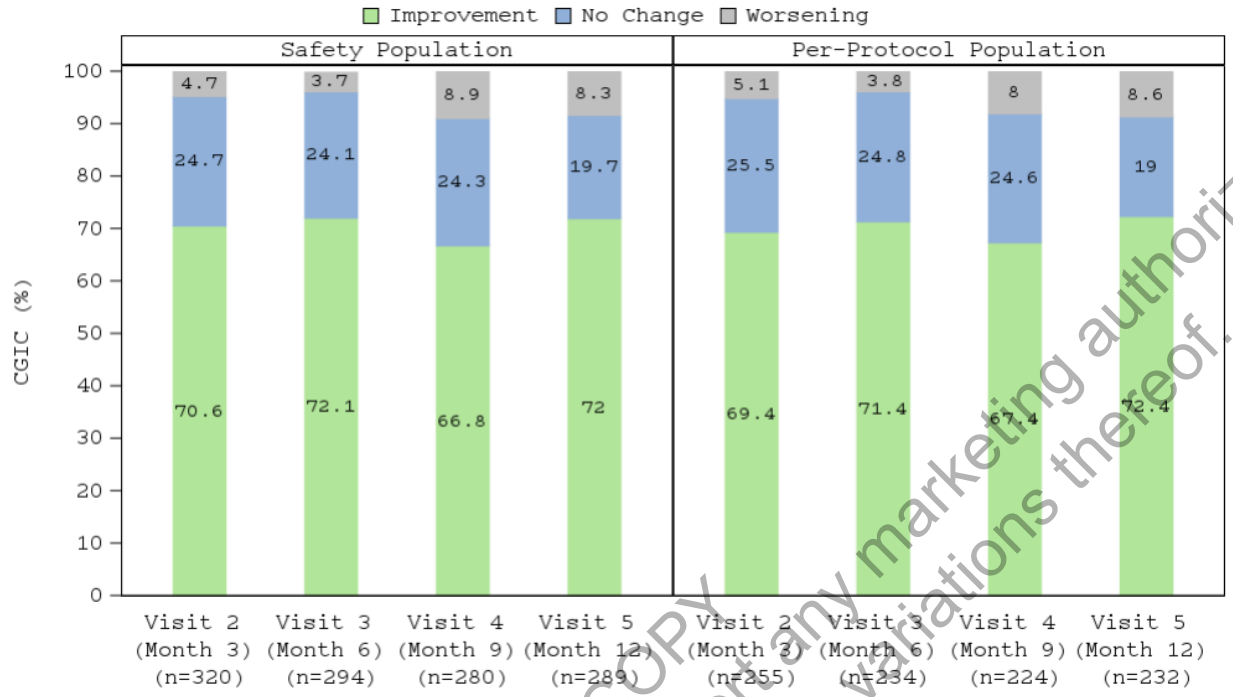
PGIC=Patient Global Impression of Change; PPS=Per Protocol Set; SS=Safety Set.
Note: The PGIC describes how the patient felt over the past 4 weeks compared with before they entered the study and was assessed at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9) and Visit 5 (Month 12) according to 7 categories (1=Very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse). The above 7 categories of PGIC are collapsed into 3 categories: Improvement (category 1, 2 or 3), No change (category 4), Worsening (category 5, 6 or 7).
Source: Figure 3.1

The PGIC was completed by 211 (53.8%) patients in the SS and 179 (58.9%) patients in the PPS at Visit 5 (Month 12). Results for the SS showed that the majority of these patients reported any improvement (66.8%), while 26.1% reported no change, and 7.1% reported any worsening. One (0.5%) patient reported the condition as very much worse. The proportion of patients who reported any improvement, no change, or any worsening was generally comparable across all visits throughout the study. The results were comparable in the PPS (Table 6.11.1 and Table 6.11.2).

CGIC

The CGIC described the clinician's rating of the patient's condition over the past 4 weeks compared with Baseline. Improvement in the clinical condition was stable over time during the observational period of the study (Figure 10-4).

Figure 10-4: CGIC from Baseline by Visit (SS and PPS)



CGIC=Clinical Global Impression of Change; PPS=Per Protocol Set; SS=Safety Set.
Note: The CGIC describes the clinician's assessment of the patient's condition over the past 4 weeks compared with Baseline (as assessed by the treating physician) and was assessed at Visit 2 (Month 3), Visit 3 (Month 6), Visit 4 (Month 9), and Visit 5 (Month 12) according to 7 categories (1=Very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse). The above 7 categories of CGIC are collapsed into 3 categories: Improvement (category 1, 2 or 3), No change (category 4), Worsening (category 5, 6 or 7).
Source: Figure 3.2

The treating physicians completed the CGIC for 289 (73.7%) patients in the SS and 232 (76.3%) patients in the PPS at Visit 5 (Month 12). Similar to the PGIC, results for the CGIC in the SS showed that most of these patients were considered to have any improvement in clinical condition (72.0%). Fewer patients were assessed as showing no change (19.7%) or any worsening (8.3%). Of those considered to have worsened, the clinical condition of 2 patients (0.7%) was assessed as very much worse. The proportion of patients with any improvement, no change, or any worsening was sustained throughout the study timepoints. The results were comparable in the PPS (Table 6.10.1 and Table 6.10.2).

10.3.4.2 QOLIE-10-P

The observed QOLIE-10-P total score at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 5 (Month 12) and change from Baseline is presented in Table 10-31. Overall, the change from Baseline in the QOLIE-10-P total score showed mean increases up to Visit 5 (Month 12) for the SS, indicating that the patients who contributed to these data had an improvement in their quality of life, and this mean change increased over time (Figure 3.3).

The observed QOLIE-10-P epilepsy distress score at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 5 (Month 12) and change from Baseline is also presented in Table 10-31. Mean (SD) change from Baseline in the epilepsy distress score showed numerical increases up to Visit 5

(Month 12) in the SS (20.19 [32.05]), indicating lower level of distress experienced by these patients.

Table 10-31: QOLIE-10-P total and epilepsy distress scores observed results and changes from Baseline (SS)

Type of score Visit	All patients N=392					
	Observed results			Change from Baseline		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Total score						
Visit 1 (Baseline)	294	53.62 (18.51)	53.92 (40.50, 67.17)	NA	NA	NA
Visit 3 (Month 6)	197	63.65 (16.89)	65.33 (52.41, 77.33)	178	6.79 (16.12)	4.67 (−3.50, 16.17)
Visit 5 (Month 12)	173	64.47 (19.34)	67.67 (49.50, 80.17)	152	9.86 (17.99)	8.59 (−1.17, 21.17)
[redacted]						
Visit 1 (Baseline)	303	49.37 (26.91)	50.00 (25.00, 75.00)	NA	NA	NA
Visit 3 (Month 6)	198	63.61 (26.43)	75.00 (50.00, 75.00)	181	12.71 (30.19)	0.00 (0.00, 25.00)
Visit 5 (Month 12)	176	68.47 (28.63)	75.00 (50.00, 100.00)	160	20.19 (32.05)	25.00 (0.00, 50.00)

NA=not applicable; Q1=25th Percentile; Q3=75th Percentile; QOLIE=Quality of Life Inventory in Epilepsy; SD=standard deviation; SS=Safety Set.
Note: The QOLIE-10-P total score ranges from 0 to 100 with higher scores indicating better functioning. The [redacted]
Note: The total score was calculated as the sum of the 10 items scores of the QOLIE-10-P divided by the number of answered items as long as there was no more than 1 missing response. In the case where there was more than 1 of the 10 QOLIE-10-P items scores missing, then the QOLIE-10-P score was missing.
Note: The change from Baseline at each visit for the total score and epilepsy distress score was calculated as: Total score/[redacted] at post-Baseline Visit – Total score/[redacted] at Visit 1 (Baseline).
Source: Table 6.12.1

The mean change from Baseline in the QOLIE-10-P total score increased steadily over time, indicating an improvement in health-related quality of life for patients in both the SS and the PPS (Figure 3.3 and Figure 3.4). A similar trend was observed for the [redacted] indicating decreased stress.

The observed results related to the QOLIE-10-P total and [redacted] in the PPS were comparable to the results in the SS (Table 6.12.2 and Figure 3.4).

10.3.4.3 TSQM-9

The observed TSQM-9 scores for each domain are described for the SS below in Table 10-32 along with the change from Baseline. Overall, there was a general trend of steady mean increase in scores over time for all 3 domains (Figure 3.5), indicating improvement throughout the study in patient perceived effectiveness, convenience, and global satisfaction with adjunctive brivaracetam treatment upon the initiation of the new therapy regime.

Table 10-32: TSQM-9 observed results and changes from Baseline (SS)

	All patients N=392					
	Observed results			Change from Baseline		
Domain of TSQM-9 Visit	**n**	**Mean (SD)**	**Median (Q1, Q3)**	**n**	**Mean (SD)**	**Median (Q1, Q3)**
Effectiveness (Question 1 to 3)						
Visit 1 (Baseline)	269	51.49 (23.54)	50.00 (33.33, 66.67)	NA	NA	NA
Visit 2 (Month 3)	234	62.78 (23.03)	66.67 (50.00, 83.33)	176	10.78 (31.48)	5.56 (-5.56, 27.78)
Visit 3 (Month 6)	213	65.60 (24.08)	66.67 (50.00, 83.33)	164	15.09 (28.65)	11.11 (-5.56, 33.33)
Visit 4 (Month 9)	179	66.82 (24.22)	66.67 (50.00, 88.89)	138	16.83 (30.30)	16.67 (-5.56, 38.89)
Visit 5 (Month 12)	182	71.15 (22.57)	72.22 (55.56, 88.89)	144	21.57 (29.59)	22.22 (0.00, 38.89)
Convenience (Question 4 to 6)						
Visit 1 (Baseline)	272	75.65 (19.33)	77.78 (63.89, 91.67)	NA	NA	NA
Visit 2 (Month 3)	234	80.59 (17.03)	83.33 (66.67, 100.00)	178	3.14 (18.79)	0.00 (-5.56, 11.11)
Visit 3 (Month 6)	212	82.08 (15.60)	83.33 (66.67, 100.00)	166	3.28 (16.44)	0.00 (-5.56, 11.11)
Visit 4 (Month 9)	178	83.52 (15.47)	83.33 (72.22, 100.00)	139	6.63 (16.80)	5.56 (0.00, 16.67)
Visit 5 (Month 12)	182	83.82 (14.82)	83.33 (72.22, 100.00)	146	6.05 (17.05)	5.56 (-5.56, 16.67)
Global Satisfaction (Question 7 to 9)						
Visit 1 (Baseline)	270	53.85 (24.04)	57.14 (35.71, 71.43)	NA	NA	NA

Table 10-32: TSQM-9 observed results and changes from Baseline (SS)

Domain of TSQM-9 Visit	All patients N=392					
	Observed results			Change from Baseline		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Visit 2 (Month 3)	234	63.34 (23.11)	64.29 (50.00, 78.57)	176	9.38 (27.05)	7.14 (-7.14, 25.00)
Visit 3 (Month 6)	213	67.17 (23.58)	71.43 (50.00, 85.71)	165	11.17 (28.91)	7.14 (-7.14, 28.57)
Visit 4 (Month 9)	179	69.70 (22.37)	71.43 (50.00, 85.71)	139	15.68 (28.89)	14.29 (0.00, 35.71)
Visit 5 (Month 12)	182	71.74 (23.48)	78.57 (50.00, 92.86)	145	19.06 (27.83)	14.29 (0.00, 35.71)

NA=not applicable; Q1=25th Percentile; Q3=75th Percentile; SS=Safety Set; TSQM-9=Treatment Satisfaction Questionnaire for Medication-9.

Note: TSQM-9 includes 9 items and 3 domains (reported by the patients): Effectiveness (Questions 1 to 3), Convenience (Questions 4 to 6), and Global Satisfaction (Questions 7 to 9). Scores for each domain were computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100, where higher values indicate higher effectiveness, convenience, or satisfaction. Of note, a score could be computed for a domain only if no more than 1 item was missing from that domain.

Source: Table 6.13.1

The observed results related to the TSQM-9 scores for each domain in the PPS were comparable to the results in the SS (Table 6.13.2 and Figure 3.6).

10.3.4.4 WPAI:GH

The observed WPAI:GH scores for each dimension are presented for the SS below in Table 10-33 along with the change from Baseline. Overall, there was a decrease in mean score changes from Baseline across all dimensions indicating improved patient activity and work impairment, better productivity, and less work time missed over time within the study observational period compared with the period prior to initiating adjunctive brivaracetam treatment. Notably, some subscales were reported only by patients with a job.

Table 10-33: WPAI:GH observed results and changes from Baseline (SS)

Dimensions of WPAI:GH Visit	All patients N=392					
	Observed results			Change from Baseline		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Percent work time missed due to health problem [a]						
Visit 1 (Baseline)	113	19.47 (33.88)	0.00 (0.00, 23.68)	NA	NA	NA
Visit 2 (Month 3)	85	8.29 (21.05)	0.00 (0.00, 0.00)	64	-13.57 (41.72)	0.00 (-26.18, 0.00)
Visit 3 (Month 6)	77	9.70 (23.50)	0.00 (0.00, 6.25)	60	-7.62 (44.86)	0.00 (-13.06, 0.00)
Visit 4 (Month 9)	71	10.78 (24.68)	0.00 (0.00, 7.50)	49	-12.44 (46.84)	0.00 (-27.24, 0.00)
Visit 5 (Month 12)	70	8.50 (20.50)	0.00 (0.00, 0.00)	50	-12.29 (38.31)	0.00 (-20.00, 0.00)
Percent impairment while working due to health problem [b]						
Visit 1 (Baseline)	143	31.26 (31.35)	20.00 (0.00, 50.00)	NA	NA	NA
Visit 2 (Month 3)	102	19.41 (13.87)	10.00 (0.00, 30.00)	79	-7.34 (29.47)	0.00 (-20.00, 10.00)
Visit 3 (Month 6)	88	20.11 (26.41)	10.00 (0.00, 30.00)	73	-7.12 (34.50)	0.00 (-20.00, 10.00)
Visit 4 (Month 9)	82	21.34 (27.92)	10.00 (0.00, 30.00)	63	-6.19 (34.61)	0.00 (-20.00, 10.00)
Visit 5 (Month 12)	83	18.31(25.84)	0.00 (0.00, 30.00)	63	-7.78 (34.57)	0.00 (-20.00, 10.00)
Percent overall work impairment due to health problem [c]						
Visit 1 (Baseline)	111	39.51 (34.68)	30.00 (10.00, 70.00)	NA	NA	NA
Visit 2 (Month 3)	84	27.02 (27.97)	20.00 (0.00, 50.00)	61	-10.72 (39.70)	-10.00 (-23.17, 10.00)
Visit 3 (Month 6)	77	26.89 (31.96)	10.00 (0.00, 46.38)	58	-6.43 (43.79)	-7.96 (-30.00, 14.10)
Visit 4 (Month 9)	71	27.58 (33.04)	10.00 (0.00, 48.72)	47	-9.16 (41.34)	-10.00 (-28.00, 10.00)

Table 10-33: WPAI:GH observed results and changes from Baseline (SS)

Dimensions of WPAI:GH Visit	All patients N=392					
	Observed results			Change from Baseline		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Visit 5 (Month 12)	70	26.32 (32.09)	10.00 (0.00, 50.00)	48	-9.02 (38.56)	-4.96 (-22.30, 9.38)
Percent activity impairment due to health problem [d]						
Visit 1 (Baseline)	301	40.66 (31.31)	40.00 (10.00, 70.00)	NA	NA	NA
Visit 2 (Month 3)	222	31.35 (30.02)	20.00 (0.00, 50.00)	189	-6.88 (30.62)	0.00 (-20.00, 10.00)
Visit 3 (Month 6)	206	28.06 (29.02)	20.00 (0.00, 50.00)	183	-10.66 (31.35)	0.00 (-30.00, 10.00)
Visit 4 (Month 9)	172	24.71 (26.10)	20.00 (0.00, 40.00)	150	-13.27 (31.74)	-10.00 (-40.00, 10.00)
Visit 5 (Month 12)	176	27.05 (29.11)	20.00 (0.00, 50.00)	157	-14.01 (34.49)	-10.00 (-40.00, 0.00)

NA=not applicable; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set; WPAI:GH=Work Productivity and Activity Impairment Questionnaire: General Health
Note: WPAI:GH scores range between 0 and 100, with higher numbers indicating greater impairment and lower productivity.
[a] Percent work time missed due to health problem: (question 2 hours/[question 2 hours + question 4 hours]) *100.
[b] Percent impairment while working due to health problem: (question 5 score/10) *100.
[c] Percent overall work impairment due to health problem: (question 2 hours/[question 2 hours + question 4 hours] + [(1-[question 2 hours/(question 2 hours + question 4 hours)]) x (question 5 score/10)]) *100.
[d] Percent activity impairment due to health problem: (question 6 score/10) *100.
Source: Table 6.14.1

The observed results related to the WPAI:GH scores for each dimension in the PPS were comparable to results in the SS (Table 6.14.2).

10.3.4.5 NDDI-E

The observed NDDI-E total score at Visit 1 (Baseline), Visit 3 (Month 6), and Visit 5 (Month 12) are presented for the SS below in Table 10-34 along with the change from Baseline. Small numerical decreases in median values were observed over time, indicating slight improvements in depressive symptoms in patients contributing to these analyses.

Table 10-34: NDDI-E observed results and changes from Baseline (SS)

Visit	All patients N=392					
	Observed results			Change from Baseline		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Visit 1 (Baseline)	308	12.85 (4.43)	13.00 (9.00, 16.00)	NA	NA	NA
Visit 3 (Month 6)	205	11.40 (4.27)	11.00 (8.00, 14.00)	186	-0.78 (4.17)	0.00 (-3.00, 1.00)
Visit 5 (Month 12)	175	11.05 (4.49)	10.00 (7.00, 14.00)	158	-1.09 (4.13)	-1.00 (-3.00, 2.00)

NA=not applicable; NDDI-E=Neurological Disorders Depression Inventory in Epilepsy; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set.

Note: Each question from the NDDI-E has 4 response options: 4=Always or often; 3=Sometimes; 2=Rarely; 1=Never. NDDI-E score was calculated as the sum of the scores from question 1 to question 6 (all questions needed to be complete to generate the NDDI-E score, otherwise the total score was missing). The NDDI-E score ranges from 6-24, with higher scores reflecting more severe depressive symptoms and a score of >15 suggesting a possible major depressive disorder.

Source: Table 6.16.1

The observed results related to the NDDI-E in the PPS were comparable to results obtained in the SS (Table 6.16.2).

10.3.4.6 SSQ

A modified version of the SSQ was used in the study (see Section 9.4.3.2.1). The results for question 5 ([redacted]) are presented for the SS in Table 10-35, and results related to the 3 subquestions are presented in Table 6.15.1. At Baseline, 63.6% (196/308) of patients in the SS who completed the modified SSQ reported having cognitive effects after seizures. This proportion decreased over the study period, especially in the first 3 months, and this proportion remained low at Visit 5 (Month 12) (37.0% [50/135] of patients) compared to Baseline.

In patients who had cognitive effects after seizures, the mean scores related to the frequency, severity, and bothersomeness of these cognitive effects tended to be slightly reduced over time (Table 6.15.1). The SSQ results for question 5, including 3 subquestions, were comparable in the PPS (Table 6.15.2).

Table 10-35: SSQ observed results for question 5 (SS)

[redacted]	Statistic	All patients N=392
		Observed results
Visit 1 (Baseline)	n (%)	308 (78.6)
Yes	n (%)	196 (63.6)
No	n (%)	112 (36.4)
Visit 2 (Month 3)	n (%)	211 (53.8)
Yes	n (%)	89 (42.2)
No	n (%)	122 (57.8)
Visit 3 (Month 6)	n (%)	189 (48.2)
Yes	n (%)	76 (40.2)
No	n (%)	113 (59.8)
Visit 4 (Month 9)	n (%)	156 (39.8)
Yes	n (%)	55 (35.3)
No	n (%)	101 (64.7)
Visit 5 (Month 12)	n (%)	135 (34.4)
Yes	n (%)	50 (37.0)
No	n (%)	85 (63.0)

SS=Safety Set; SSQ=Seizure Severity Questionnaire.
Note: A modified version of the SSQ was used that was comprised only of question 5 (with 3 subquestions 5A, 5B, and 5C) and question 8.
Note: [redacted]
Source: Table 6.15.1

The shifts from Baseline in responses to question 5 of the SSQ are presented in Table 10-36. For most patients, the occurrence of postictal cognitive effects did not change between prior to brivaracetam initiation and post-Baseline assessments. For patients with Baseline and Visit 5 (Month 12) SSQ data, 35.3% of patients did not have postictal cognitive effects at either timepoint, and 28.6% of patients had postictal cognitive effects at both time points. The proportion of patients who had postictal cognitive effects at Baseline and none at Visit 5 (Month 12) was 31.1%, while the proportion of patient with no postictal cognitive effects at

Baseline and some postictal cognitive effects at Visit 5 (Month 12) was 5.0%. The shift from Baseline was comparable in the PPS (Table 6.15.4).

Table 10-36: Shift from Baseline in SSQ of question 5 (SS)

Visit	[redacted]	Post-Baseline Assessment		
		Yes n (%)	No n (%)	Total n (%)
Visit 2 (Month 3)	Yes	63 (33.9)	47 (25.3)	110 (59.1)
	No	14 (7.5)	62 (33.3)	76 (40.9)
	Total	77 (41.4)	109 (58.6)	186 (100)
Visit 3 (Month 6)	Yes	59 (33.5)	44 (25.0)	103 (58.5)
	No	11 (6.3)	62 (35.2)	73 (41.5)
	Total	70 (39.8)	106 (60.2)	176 (100)
Visit 4 (Month 9)	Yes	40 (28.8)	40 (28.8)	80 (57.6)
	No	9 (6.5)	50 (36.0)	59 (42.4)
	Total	49 (35.3)	90 (64.7)	139 (100)
Visit 5 (Month 12)	Yes	34 (28.6)	37 (31.1)	71 (59.7)
	No	6 (5.0)	42 (35.3)	48 (40.3)
	Total	40 (33.6)	79 (66.4)	119 (100)

SS=Safety Set; SSQ=Seizure Severity Questionnaire.
Note: A modified version of the SSQ was used that was comprised only of question 5 (with 3 subquestions 5A, 5B, and 5C) and question 8.
Note: [redacted]
Source: Table 6.15.3

The observed results for question 8 of the SSQ (overall severity of seizures) are presented in Table 10-37. Overall, there was improvement through Month 6 in mean and median values. Mean values continued to slightly decrease and median values remained stable thereafter.

Table 10-37: SSQ observed results for question 8 (SS)

[redacted]	All patients N=392		
	Observed results		
	n	Mean (SD)	Median (Q1, Q3)
Visit 1 (Baseline)	301	3.7 (1.8)	4.0 (2.0, 5.0)
Visit 2 (Month 3)	198	2.8 (1.8)	3.0 (1.0, 4.0)
Visit 3 (Month 6)	173	2.7 (1.7)	2.0 (1.0, 4.0)
Visit 4 (Month 9)	149	2.5 (1.7)	2.0 (1.0, 4.0)
Visit 5 (Month 12)	124	2.4 (1.6)	2.0 (1.0, 4.0)

PPS=Per Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set; SSQ=Seizure Severity Questionnaire.
Note: A higher score reflects a worse outcome.
Source: Table 6.15.1

10.3.5 Safety variables

10.3.5.1 Brivaracetam exposure

During this study, the mean (SD) duration of brivaracetam exposure for the SS was 310.8 (125.7) days, and the median (Q1, Q3) duration was 365.0 (332.0, 372.0) days. Duration of brivaracetam exposure was ≥12 months (≥360 days) for 62.0% (243/392) of patients. Two patients had brivaracetam exposure of 20 months or more, and 4 patients had brivaracetam exposure between 15 to 17 months. Similar results were observed in the PPS (Table 8.1.1 and Table 8.1.2).

The daily dosing categories by timepoint for brivaracetam for the SS are presented below in Table 10-38. At Visit 1 (Baseline), 11.2% of patients were dosed at >10 to <50mg/day. The majority of patients were dosed at 50 to 200mg/day (the approved SmPC range), and this percentage increased at subsequent visits. The percentages of patients dosed in the ≥150 to ≤200mg/day and >200mg/day categories increased over time from 11.2% to 37.2% and 1.0% to 4.0%, respectively, from Visit 1 (Baseline) to Visit 5 (Month 12). At Visit 1 (Baseline), the highest percentages of patients were in the ≥50 to <100mg/day (41.1%) and ≥100 to <150mg/day (35.5%) dosing categories. At Visit 5 (Month 12), the highest percentages of patients were in the ≥100 to <150mg/day (37.6%) and ≥150 to ≤200mg/day (37.2%) dosing categories.

Table 10-38: Brivaracetam daily dosing categories by timepoint (SS)

All patients N=392 n (%)					
BRV daily dosing	**Visit 1 (Baseline)**	**Visit 2 (Month 3)**	**Visit 3 (Month 6)**	**Visit 4 (Month 9)**	**Visit 5 (Month 12)**
Dosing categories					
≤10mg	0	0	1 (0.3) [a]	0	0
>10mg to <50mg	44 (11.2)	5 (1.5)	1 (0.3)	0	0
≥50mg to <100mg	161 (41.1)	82 (24.8)	70 (22.8)	62 (21.7)	63 (21.1)
≥100mg to <150mg	139 (35.5)	148 (44.7)	127 (41.4)	118 (41.3)	112 (37.6)
≥150mg to ≤200mg	44 (11.2)	89 (26.9)	97 (31.6)	98 (34.3)	111 (37.2)
>200mg	4 (1.0)	7 (2.1)	11 (3.6)	8 (2.8)	12 (4.0)

BRV=brivaracetam; SS=Safety Set.
Note: If a patient had multiple brivaracetam records at or around the same visit, the dosing records at or closest to the scheduled visit date were presented and summarized for the following descriptive statistics.
Note: Percentages were based on the nonmissing data per visit.
[a] This patient was on brivaracetam 10mg/day at Visit 3 during down titration.
Source: Table 8.2.1

Daily dosing categories are presented by timepoint for the PPS in Table 8.2.2. Two patients who received a single brivaracetam dose below 50mg/day (25mg/day at Day 1) are included in the PPS. Otherwise, the PPS includes only those patients dosed within the approved SmPC range of 50 to 200mg/day (manual medical review confirmed patients' exclusion or inclusion in the PPS).

The total daily brivaracetam dose at each visit is summarized for the SS and the PPS in Table 10-39. The mean daily dose increased over time. The median dose at Visit 1 (Baseline) was 50mg/day in the SS, which then increased to 100mg/day for the remainder of the study (Visit 2 through Visit 5). The median dose in the PPS was 100mg/day throughout the study.

Table 10-39: Brivaracetam total daily dose summary at each visit (SS and PPS)

Variable	**Statistic**	**All patients (SS) N=392**	**All patients (PPS) N=304**
Total daily dose at Visit 1 (Baseline) (mg/day)	n	392	304
	Mean (SD)	82.2 (49.8)	85.6 (42.9)

Table 10-39: Brivaracetam total daily dose summary at each visit (SS and PPS)

Variable	Statistic	All patients (SS) N=392	All patients (PPS) N=304
	Median (Q1, Q3)	50.0 (50.0, 100.0)	100.0 (50.0, 100.0)
	IQR	50.0	50.0
	Min, Max	20, 300	25, 200
Total daily dose at Visit 2 (Month 3) (mg/day)	n	331	260
	Mean (SD)	114.6 (59.6)	114.0 (47.3)
	Median (Q1, Q3)	100.0 (75.0, 150.0)	100.0 (100.0, 150.0)
	IQR	75.0	50.0
	Min, Max	20, 400	50, 200
Total daily dose at Visit 3 (Month 6) (mg/day)	n	307	244
	Mean (SD)	121.8 (64.2)	117.8 (47.2)
	Median (Q1, Q3)	100.0 (100.0, 150.0)	100.0 (100.0, 150.0)
	IQR	50.0	50.0
	Min, Max	10, 500	50, 200
Total daily dose at Visit 4 (Month 9) (mg/day)	n	286	227
	Mean (SD)	125.7 (64.4)	120.4 (49.8)
	Median (Q1, Q3)	100.0 (100.0, 150.0)	100.0 (100.0, 150.0)
	IQR	50.0	50.0
	Min, Max	50, 500	50, 200
Total daily dose at Visit 5 (Month 12) (mg/day)	n	298	237
	Mean (SD)	129.9 (67.7)	123.8 (50.6)
	Median (Q1, Q3)	100.0 (100.0, 175.0)	100.0 (100.0, 150.0)
	IQR	75.0	50.0
	Min, Max	50, 500	50, 200

IQR=interquartile range; Max=maximum; Min=minimum; PPS=Per Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set.

Note: Total daily brivaracetam dose (mg/day) at a specific visit was defined as the dosing records at or closest to the scheduled visit according to the visit mapping of brivaracetam administration.
Note: If a total daily dose for a patient was across multiple visits, then this dose appears as the total daily dose for each visit.
Note: Two patients having received a single brivaracetam dose below 50mg (25mg at Day 1) are included in the PPS.
Source: Table 8.3.1, Table 8.3.2

10.3.5.2 TEAEs

An overview of incidence of TEAEs in the SS and the PPS is presented in Table 10-40. In the SS, 101 (25.8%) patients reported 215 TEAEs. Twelve (3.1%) patients reported 15 serious TEAEs. No deaths occurred. This was consistent with the PPS.

Table 10-40: Incidence of TEAEs – Overview (SS and PPS)

Category	All patients (SS) N=392 n (%) [#]	All patients (PPS) N=304 n (%) [#]
Any TEAEs	101 (25.8) [215]	68 (22.4) [121]
Serious TEAEs	12 (3.1) [15]	11 (3.6) [14]
Patient discontinuations due to TEAEs	37 (9.4) [68]	27 (8.9) [45]
Drug-related TEAEs	54 (13.8) [103]	38 (12.5) [66]
All deaths (AEs leading to death)	0	0

AE=adverse event; eCRF=electronic Case Report Form; PPS=Per Protocol Set; SS=Safety Set; TEAE=treatment-emergent adverse event.
Note: A TEAE was defined as an AE occurring on or after the date of first brivaracetam administration up to 4 weeks (28 days) after brivaracetam discontinuation.
Note: n=number of patients reporting at least 1 TEAE in that category. [#] is the number of individual occurrences of the TEAE in that category. Percentages are based on the number of patients in the SS or PPS.
Note: All deaths refers to all deaths occurring on study.
Note: The patients with a response of "Related" for the question of "Related to Study Medication" on the Adverse Events eCRF were counted into this table; missing relatedness was excluded.
Note: Patient discontinuations due to TEAEs is based on TEAEs leading to discontinuation of brivaracetam medication.
Source: Table 9.1.1, Table 9.1.2

An overview of the incidence of TEAEs by SOC and PT occurring in ≥2% of patients in the SS and the PPS is presented in Table 10-41. In the SS, the top 3 SOCs with the most frequently reported TEAEs were nervous system disorders (47 [12.0%] patients), psychiatric disorders (46 [11.7%] patients), and general disorders and administration site conditions (24 [6.1%] patients). The 3 most common TEAEs were fatigue (20 [5.1%] patients), followed by seizure (12 [3.1%] patients) and dizziness (12 [3.1%] patients). The results in the PPS were comparable with the SS.

Table 10-41: Incidence of TEAEs occurring in ≥2% of SS or PPS patients by PT (SS and PPS)

MedDRA 18.1 SOC PT	All patients (SS) N=392 n (%) [#]	All patients (PPS) N=304 n (%) [#]
Any TEAE	101 (25.8) [215]	68 (22.4) [121]
General disorders and administration site conditions	24 (6.1) [25]	14 (4.6) [14]
Fatigue	20 (5.1) [20]	10 (3.3) [10]
Infections and infestations	15 (3.8) [15]	10 (3.3) [10]
Corona virus infection	10 (2.6) [10]	7 (2.3) [7]
Nervous system disorders	47 (12.0) [58]	28 (9.2) [32]
Dizziness	12 (3.1) [13]	6 (2.0) [7]
Seizure	12 (3.1) [13]	9 (3.0) [9]
Somnolence	10 (2.6) [10]	5 (1.6) [5]
Headache	9 (2.3) [9]	3 (1.0) [3]
Psychiatric disorders	46 (11.7) [67]	29 (9.5) [38]
Anxiety	11 (2.8) [12]	7 (2.3) [8]
Irritability	8 (2.0) [8]	5 (1.6) [5]

MedDRA=Medical Dictionary for Regulatory Activities; PPS=Per Protocol Set; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event.
Note: n=number of patient reporting at least 1 TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the TEAE.
Source: Table 9.2.1, Table 9.2.2

The only PT occurring in at least 5% of patients was fatigue (5.1% in the SS; 3.3% in the PPS) (Table 9.2.3 and Table 9.2.2). No PT occurred in at least 5% of patients in the PPS (Table 9.2.4).

10.3.5.3 Behavioral TEAEs

Twelve (3.1%) patients in the SS experienced 14 behavioral TEAEs with PTs of irritability (8 [2.0%] patients), aggression (2 [0.5%] patients), agitation (2 [0.5%] patients), and affect lability (1 [0.3%] patient). The most frequently reported behavioral TEAE was irritability (8 [2.0%] patients reported 8 events). The results in the PPS were comparable with the SS (Table 9.3.1 and Table 9.3.2).

10.3.5.4 Serious TEAEs

A summary of the incidence of serious TEAEs in the SS and the PPS is provided in Table 10-42. In the SS, 12 (3.1%) patients experienced 15 serious TEAEs. The most frequently reported serious TEAEs by SOC were nervous system disorders (6 [1.5%] patients), injury, poisoning, and procedural complications (2 [0.5%] patients), and psychiatric disorders and neoplasms benign, malignant, and unspecified (including cysts and polyps) (each reported by 2 [0.5%] patients).

The most frequently reported serious TEAEs (by PT) were seizure (3 [0.8%] patients) and partial seizures with secondary generalization (2 [0.5%] patients). No other serious TEAEs were reported in more than 1 patient.

The results in the PPS were comparable with the SS.

Table 10-42: Incidence of Serious TEAEs by SOC and PT (SS and PPS)

MedDRA 18.1 SOC PT	All patients (SS) N=392 n (%) [#]	All patients (PPS) N=304 n (%) [#]
Any Serious TEAE	12 (3.1) [15]	11 (3.6) [14]
Congenital, familial and genetic disorders	1 (0.3) [1]	1 (0.3) [1]
Cortical dysplasia	1 (0.3) [1]	1 (0.3) [1]
Injury, poisoning and procedural complications	2 (0.5) [3]	2 (0.7) [3]
Dislocation of vertebra	1 (0.3) [1]	1 (0.3) [1]
Fall	1 (0.3) [1]	1 (0.3) [1]
Hand fracture	1 (0.3) [1]	1 (0.3) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.5) [2]	1 (0.3) [1]
Anogenital warts	1 (0.3) [1]	0
Brain neoplasm	1 (0.3) [1]	1 (0.3) [1]
Nervous system disorders	6 (1.5) [7]	6 (2.0) [7]
Seizure	3 (0.8) [3]	3 (1.0) [3]
Partial seizures with secondary generalization	2 (0.5) [2]	2 (0.7) [2]
Change in seizure presentation	1 (0.3) [1]	1 (0.3) [1]
Dementia Alzheimer's type	1 (0.3) [1]	1 (0.3) [1]
Psychiatric disorders	2 (0.5) [2]	2 (0.7) [2]
Irritability	1 (0.3) [1]	1 (0.3) [1]
Suicidal ideation	1 (0.3) [1]	1 (0.3) [1]

MedDRA=Medical Dictionary for Regulatory Activities; PPS=Per Protocol Set; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event.
Note: n=number of patient reporting at least 1 serious TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the Serious TEAE.
Source: Table 9.4.1, Table 9.4.2

10.3.5.5 Serious behavioral TEAEs

There was 1 (0.3%) patient who experienced a serious behavioral TEAE during the study (PT: irritability) (Table 9.5.1 and Table 9.5.2).

10.3.5.6 Study drug-related TEAEs

A summary of the incidence of TEAEs reported by the investigator as study drug-related in ≥2% of patients in the SS and the PPS is presented in Table 10-43.

A total of 54 (13.8%) patients in the SS experienced 103 TEAEs (events) that were study drug-related. The SOCs with the highest number of patients with study drug-related TEAEs were nervous system disorders (32 [8.2%] patients) and general disorders and administration site conditions (16 [4.1%] patients). The study drug-related TEAEs reported in ≥2% of patients were fatigue (13 [3.3%] patients), dizziness (10 [2.6%] patients), somnolence (9 [2.3%] patients), and seizure (8 [2.0%] patients).

The results in the PPS were comparable with the SS.

Table 10-43: Incidence of TEAEs reported by the investigator as study drug-related in ≥2% of SS or PPS patients by PT (SS and PPS)

MedDRA 18.1 SOC PT	All patients (SS) N=392 n (%) [#]	All patients (PPS) N=304 n (%) [#]
Any TEAE Reported by the investigator as Study Drug-related	54 (13.8) [103]	38 (12.5) [66]
General disorders and administration site conditions	16 (4.1) [16]	10 (3.3) [10]
Fatigue	13 (3.3) [13]	8 (2.6) [8]
Nervous system disorders	32 (8.2) [41]	21 (6.9) [25]
Dizziness	10 (2.6) [11]	6 (2.0) [7]
Somnolence	9 (2.3) [9]	5 (1.6) [5]
Seizure	8 (2.0) [8]	7 (2.3) [7]

eCRF=electronic Case Report Form; MedDRA=Medical Dictionary for Regulatory Activities; PPS=Per Protocol Set; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event.
Note: n=number of patient reporting at least 1 study drug-related TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the study drug-related TEAE.
Note: The patients with a response of "Related" for the question of "Related to Study Medication" on the Adverse Events eCRF were counted into this table; missing relatedness were excluded.
Source: Table 9.6.1, Table 9.6.2

10.3.5.7 Study drug-related behavioral TEAEs

Eleven (2.8%) patients in the SS experienced 13 behavioral TEAEs reported by the investigator as study drug-related (PTs: irritability [1.8%], aggression [0.5%], agitation [0.5%], affect lability [0.3%]). The most frequently reported study drug-related behavioral TEAE was irritability (7 [1.8%] patients reported 7 events). The results in the PPS were comparable with the SS (Table 9.7.1 and Table 9.7.2).

10.3.5.8 TEAEs leading to brivaracetam discontinuation

A summary of TEAEs leading to brivaracetam discontinuation in ≥2% of patients in the SS and the PPS is presented in (Table 10-44).

A total of 37 (9.4%) patients in the SS experienced 68 TEAEs that led to brivaracetam discontinuation. The most frequently reported SOCs that led to brivaracetam discontinuation were nervous system disorders (24 [6.1%] patients) and general disorders and administration site conditions (10 [2.6%] patients). The most frequently reported (≥2%) PTs that led to brivaracetam discontinuation were fatigue (9 [2.3%] patients), dizziness (9 [2.3%] patients), and seizure (8 [2.0%] patients).

Table 10-44: Incidence of TEAEs leading to brivaracetam discontinuation in ≥2% of SS or PPS patients by PT (SS and PPS)

MedDRA 18.1 SOC PT	All patients (SS) N=392 n (%) [#]	All patients (PPS) N=304 n (%) [#]
Any TEAE Leading to BRV Discontinuation	37 (9.4) [68]	27 (8.9) [45]
General disorders and administration site conditions	10 (2.6) [11]	7 (2.3) [7]
Fatigue	9 (2.3) [9]	6 (2.0) [6]
Nervous system disorders	24 (6.1) [30]	17 (5.6) [18]
Dizziness	9 (2.3) [9]	5 (1.6) [5]
Seizure	8 (2.0) [9]	6 (2.0) [6]

BRV=brivaracetam; MedDRA=Medical Dictionary for Regulatory Activities; PPS=Per Protocol Set; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event.
Note: n=number of patients reporting at least 1 TEAE leading to brivaracetam discontinuation within SOC or PT.
Note: [#] is the number of individual occurrences of the TEAE leading to brivaracetam discontinuation.
Note: Patient discontinuations due to TEAE is based on TEAEs leading to discontinuation of brivaracetam medication.
Source: Table 9.8.1, Table 9.8.2

10.3.5.9 Behavioral TEAEs leading to brivaracetam discontinuation

Five (1.3%) patients in the SS experienced 6 behavioral TEAEs that led to brivaracetam discontinuation (PTs: irritability [1.0%], aggression [0.3%], agitation [0.3%]). The most frequently reported behavioral TEAE was irritability (4 [1.0%] patients reported 4 events). The results in the PPS were comparable with the SS (Table 9.9.1 and Table 9.9.2).

10.3.5.10 AESI

There were no AESIs reported (Table 9.10.1 and Table 9.10.2).

10.3.5.11 OSR information

OSR information reported in this study was off-label use of brivaracetam (dosing not according to the recommendations of the SmPC) in the SS (32 [8.2%] patients reported 33 events) and lack of therapeutic efficacy of brivaracetam (not necessarily leading to discontinuation) in the SS and the PPS (19 [4.8%] patients reported 19 events in the SS; 13 (4.3%) patients reported 13 events in the PPS) (Table 10.1.1 and Table 10.1.2).

10.3.5.12 Pregnancies

One patient reported a pregnancy beginning approximately 3 months after receiving the first dose of brivaracetam. The patient received their last brivaracetam administration approximately 1 month after the pregnancy began and was then discontinued from the study. The study site was unable to provide any follow up related to the pregnancy outcome. Other AEs experienced by the patient were fatigue and hallucination (Listing 1.2 and Listing 8.2).

10.3.5.13 Prior AED-related AEs leading to discontinuation

Thirty-six (9.2%) patients in the SS experienced a prior AED-related AE that led to discontinuation of the respective AED. The results in the PPS were comparable with the SS (Table 9.11.1 and Table 9.11.2).

10.3.5.14 TEAEs related to the COVID-19 vaccine

There were 3 patients who experienced 5 COVID-19-vaccine-related TEAEs (Table 9.12.1 and Table 9.12.2). A summary of incidences of TEAEs excluding COVID-19-vaccine-related TEAEs is presented for the SS in Table 9.13.1 and for the PPS in Table 9.13.2. As there were few TEAEs, no further analyses were conducted.

11 DISCUSSION

The EP0103 NIS (BRITOBA) was a postmarketing, multinational, observational, prospective NIS to evaluate effectiveness, tolerability, health status, and impact on patients' quality of life of initiating adjunctive brivaracetam therapy in earlier treatment line combinations in adult patients with a history of POS. This study was designed to provide data for brivaracetam adjunctive therapy in earlier treatment line combinations and to explore how various baseline characteristics may be associated with response in earlier treatment lines in patients with POS. Each patient was followed for approximately 12 months with 5 anticipated study visits and per standard clinical practice. The treating physician exclusively determined the adjunctive brivaracetam therapy need and the treatment period.

The results of this NIS suggest that adjunctive brivaracetam is effective and well tolerated in real-world clinical practice when used in earlier treatment line combinations for patients with POS. Approximately 42% of patients in the SS were seizure free for at least 6 months within the study duration. In addition, patients benefitted from improved quality of life, better work productivity, reduced work impairment, less epilepsy distress, fewer cognitive effects after seizures, and reduced seizure severity.

Patients in subgroups with fewer lifetime AEDs, fewer concomitant AEDs, earlier adjunctive treatment lines, and lower Baseline POS frequency showed better effectiveness outcomes, as expected, compared to patients who were more refractory.

The outcomes of the study are consistent with the published results of clinical studies and other NIS, including the post-hoc analyses. The safety profile was in line with previous brivaracetam studies.

11.1 Key results

11.1.1 Study population

A total of 403 patients were enrolled at 62 sites across Germany, Italy, Spain, France, and Canada; 392 (97.3%) patients were included in the SS, and 304 (75.4%) patients were included in the PPS. At Baseline, the mean age of all patients was 44.9 years for the SS and 46.1 years for the PPS, following the selection criteria of the protocol. Around half of patients were male (52.0% for the SS; 53.3% for the PPS), and around one-third used the Helpilepsy application (34.7% for the SS; 30.3% for the PPS). The median time since first diagnosis of epilepsy was 8.37 years, and 175 (44.6%) patients had a time since first diagnosis of epilepsy of more than 10 years (SS). The median percent of life with epilepsy was 21.68%. EP0103 aimed to enroll a representative patient population with POS initiating adjunctive brivaracetam therapy in earlier treatment lines: in the SS, 29.6% patients had 1, 41.1% patients had 2, and 23.7% patients had 3 lifetime AEDs at brivaracetam initiation. This outcome was comparable with the PPS (32.2% of patients had 1, 40.1% had 2, and 26.0% had 3 lifetime AEDs).

The median (Q1, Q3) 28-day Baseline POS frequency (3 months prior to Visit 1) was 2.00 (0.67, 4.00) among the 381 (97.2%) patients with data in the SS. The median (Q1, Q3) 28-day Baseline POS with secondary generalization frequency (3 months prior to Visit 1) was 0.67 (0.33, 1.00) in the 143 (36.5%) patients in the SS who reported Baseline POS with secondary generalization. Among the 189 (48.2%) patients in the SS with known etiology, the most common (≥5% of patients) were cranial trauma (7.7%), cortical dysplasia/dysgenesis (6.1%), primary degeneration

lesion (6.1%). The most common reasons for initiating adjunctive brivaracetam were lack of efficacy of current treatment and behavioral side effects to current AED.

Of the 392 patients in the SS, 298 (76.0%) completed the 12-month observational period and 311 (79.3%) patients were prescribed brivaracetam after exiting the study.

11.1.2 Effectiveness

Overall, results from EP0103 provided supporting evidence that adjunctive brivaracetam therapy in earlier treatment lines in patients with POS is effective with a high seizure freedom rate for at least 6 consecutive months, supported by a high and stable retention rate within the 12-month observational period, consistent seizure frequency reduction, and a low rate of brivaracetam discontinuation due to lack of efficacy.

Primary variable:

- Of the patients who completed consecutive visits at least 6 months apart, 41.9% of patients in the SS and 42.2% in the PPS were seizure free for at least 6 consecutive months over the 12-month observation period.
- For subgroup analyses of the primary variable, a higher percentage of patients was seizure free for at least 6 consecutive months in subgroups with 1 to 2 lifetime AEDs, with brivaracetam in first or second adjunctive treatment lines, and Baseline POS frequency of ≤5.

Secondary variables:

- Overall, brivaracetam retention remained high throughout the study. At 12 months, 75.5% of patients in the SS and 77.0% of patients in the PPS remained on the adjunctive brivaracetam treatment.
- For the subgroup analyses, retention rates were numerically higher across the subgroups with fewer lifetime AEDs, fewer concomitant AEDs, earlier treatment lines in adjunctive therapy, and lower Baseline POS frequency. Retention rate was relatively low in the subgroup with >3 lifetime AEDs in the SS, possibly due to more refractory condition of patients.
- Seizure freedom throughout 12 months was achieved by 20.5% of patients in the SS and 19.9% of patients in the PPS.
- For the subgroup analyses, seizure freedom up to 3 and 6 months was numerically higher in subgroups of patients with 1 or 2 lifetime AEDs compared with the subgroup of patients with 3 lifetime AEDs in both the SS and the PPS. A similar trend was also observed in seizure freedom by number of treatment lines, where higher seizure freedom was observed in the subgroup with brivaracetam as first adjunctive treatment line at 3 and 6 months. Compared with subgroups with fewer lifetime AEDs and subgroups with brivaracetam as earlier treatment lines, a trend of decreasing seizure freedom at Month 9 and Month 12 was not observed in either the subgroup with 3 lifetime AEDs or the subgroup with brivaracetam as third treatment line, possibly because of the lack of ability to draw conclusions from the data due to small sample sizes, especially at later visits due to patient dropouts. Seizure freedom was higher in subgroups with <5 Baseline POS frequency over time compared with those with higher Baseline POS frequency. The highest seizure freedom was observed in the subgroup with 0 to 1 Baseline POS frequency. The outcomes in the sensitivity analysis are comparable and show no meaningful differences with the original analysis.

- Median POS frequency decreased at all timepoints (1.67 at Visit 1 [Baseline], 0.57 at Visit 2 [Month 3], 0.31 at Visit 3 [Month 6], 0.30 at Visit 4 [Month 9], and 0.00 at Visit 5 [Month 12] for the SS).
- The median absolute reduction in all types POS frequency from Baseline was >0 at all timepoints and consistent over time (0.71 at Visit 2 [Month 3], 1.00 at Visit 3 [Month 6], Visit 4 [Month 9], and Visit 5 [Month 12] for the SS). The median percent reduction from Baseline was >0 at all timepoints (68.60% at Visit 2 [Month 3], 81.33% at Visit 3 [Month 6], 82.50% at Visit 4 [Month 9] for the SS) and was 100.00% at Visit 5 (Month 12) for the SS and the PPS.
- The number and percentage of patients with a response of ≥50% seizure reduction increased over time (56.0% at Visit 2 [Month 3], 68.1% at Visit 3 [Month 6], 68.7% at Visit 4 [Month 9] in the SS) with the highest percentage occurring at Visit 5 (Month 12) (75.7% in the SS; 77.6% in the PPS).
- Seventeen (4.3%) patients in the SS discontinued brivaracetam due to lack of efficacy, and 12 (3.9%) patients in the PPS discontinued brivaracetam due to lack of efficacy.

11.1.3 Other effectiveness variables

- For the patients using Helpilepsy to report seizures (n=134 for the SS; n=90 for the PPS), the median number of all types of seizures was 0.0 at all timepoints.
- The median time to first seizure in patients using Helpilepsy was 82.0 days in the SS and 143.0 days in the PPS.

11.1.4 Health outcomes

- For the CGIC, physicians reported any improvement in clinical condition over the past 4 weeks compared with Baseline for 72.0% of patients in the SS at Month 12, while no change was reported for 19.7% of patients. For the PGIC, 66.8% of patients in the SS reported any improvement at Month 12, while 26.1% reported no change.
- The change from Baseline in the QOLIE-10-P total score showed mean increases up to Month 12, indicating improvement in quality of life. A similar trend was observed in the epilepsy distress score.
- The observed TSQM-9 mean scores showed a trend of steady increase in all 3 domain score changes from Baseline over time, indicating improvement throughout the study in patient-perceived effectiveness, convenience, and global satisfaction with adjunctive brivaracetam treatment upon the initiation of the new therapy regime.
- The observed WPAI:GH mean scores showed a decrease in scores from Baseline across all dimensions, indicating improved patient activity and work impairment, better productivity, and less work time missed over time upon initiating adjunctive brivaracetam treatment. Notably, some subscales were reported only by patients with a job.
- The observed NDDI-E total score showed small numerical decreases in median values from Baseline, suggesting a reduction in depressive symptoms.
- Per question 5 of the SSQ, the number and percentage of patients who reported the presence of cognitive effects (yes/no) after seizures decreased over time. In patients who had cognitive

effects after seizures, the mean scores related to the frequency, severity, and bothersomeness of these cognitive effects tended to be slightly reduced over time. For question 8 of the SSQ, there was improvement through Month 6 in mean and median values. Mean values continued to slightly decrease and median values remained stable thereafter.

11.1.5 Safety variables

Overall, the results from EP0103 show that brivaracetam is well tolerated as an adjunctive therapy used in earlier treatment lines, as indicated by a low incidence of serious TEAEs, study drug-related TEAEs, and TEAEs that led to discontinuation. There is no new safety signal detected in this study. Results between the SS and the PPS were comparable. The following results are presented for the SS:

- The median total daily dose at Visit 1 (Baseline) was 50.0mg/day, which then increased to 100.0mg/day for the remainder of the study (Visit 2 through Visit 5).
- Overall, 101 (25.8%) patients reported 215 TEAEs. The most common TEAE was fatigue (20 [5.1%] patients).
- Twelve (3.1%) patients experienced 15 serious TEAEs. The most frequently reported serious TEAE by PT was seizure (3 [0.8%] patients).
- Study drug-related TEAEs occurred in 54 (13.8%) patients. The most frequently reported PT was fatigue (13 [3.3%] patients).
- There were 37 (9.4%) patients who experienced 68 TEAEs that led to brivaracetam discontinuation. The most frequently reported PTs that led to brivaracetam discontinuation were fatigue and dizziness (each reported by 9 [2.3%] patients).
- Behavioral TEAEs occurred in 12 (3.1%) patients. There was 1 (0.3%) patient who experienced a serious behavioral TEAE during the study (PT: irritability). Eleven (2.8%) patients experienced 13 study drug-related non-serious behavioral TEAEs (PTs: irritability [1.8%], aggression [0.5%], agitation [0.5%], affect lability [0.3%]). Five (1.3%) patients experienced 6 behavioral TEAEs that led to brivaracetam discontinuation (PTs: irritability [1.0%], aggression [0.3%], agitation [0.3%]). Overall, the most frequently reported behavioral TEAE was irritability (8 [2.0%] patients).
- One (0.3%) patient reported 1 pregnancy.
- There were no deaths during the study.

11.2 Limitations

All biases mentioned in Section 9.6 represent limitations of this study (recall bias, site selection bias, patient selection bias, nonresponse bias).

11.2.1 Interpretation

The EP0103 NIS (BRITOBA) is the largest real-world study to date that showed that brivaracetam adjunctive therapy is effective and well tolerated when administered in patients in earlier treatment line combinations. The seizure freedom rate, reduction in POS, 50% or greater responder rate, and retention on therapy results upon initiation of adjunctive brivaracetam treatment suggest that adding brivaracetam in earlier adjunctive therapy combinations is an

effective treatment for patients with POS, supporting improved quality of life and clinical condition status, and reducing activity impairment due to health problems and depressive symptoms. The patient's global satisfaction after the initiation of the adjunctive brivaracetam treatment increased over the observational period of the study. The safety profile was in line with previously conducted real-world studies and the SmPC data.

The outcomes of this observational study are in line with the published results from earlier phase studies, for example, the post-hoc analysis of a randomized, double-blind, placebo-controlled clinical Phase 3 study (Brandt et al, 2023), where the higher 12-month retention and continuous seizure freedom were observed in subgroup with fewer lifetime AEDs. Similar findings were also observed in other real-world data (Martin et al, 2023; Villanueva et al, 2023).

11.3 Generalizability

The results of this EP0103 NIS are generalizable for patients with POS treated with adjunctive brivaracetam in earlier treatment lines, though the limitations of the real-world study design are to be considered.

EP0103 NIS had a large sample size, continuous enrollment, less restrictive selection criteria (eg, no exclusion of patients based on comorbidities), and a relatively long follow up period of 12 months. Additionally, the study had a low discontinuation rate and limited missing data, which contributed to the large number of patients who remained in the study and were included in the analyses. Collectively, these aspects of the EP0103 study design and study outcomes provided a [redacted] outcome that is representative of the population of interest.

Since the completion of the patient-reported questionnaires was voluntary and this data had different collection methods, eg, patients completing the questionnaires via the Helpilepsy application and responses recorded on paper questionnaires by the physician via phone call with the patient, variation in data sources and data only being available for a portion of the patients at later visits could have limited the generalizability of these results.

12 OTHER INFORMATION

A by-country analysis was originally planned, but due to unequal distributions of patients across countries, this analysis was not performed. The number of enrolled patients varied greatly between countries, ranging in the APD from 8 patients in Canada to 172 patients in Germany.

13 CONCLUSION

The outcomes of this NIS to evaluate the effectiveness of adjunctive brivaracetam in earlier treatment line combinations in patients with POS yield the following conclusions:

- The primary endpoint, seizure freedom for at least 6 consecutive months, was achieved by 41.9% of patients over the 12-month observation period, and continuous seizure freedom was reported for 12 months in 20.5% of patients (SS).
- Retention of brivaracetam therapy remained high, and the discontinuation of brivaracetam due to lack of efficacy was low. Median POS frequency decreased at all timepoints from Baseline to Month 12, and the majority of patients achieved ≥50% seizure reduction at Month 12.

- Improvements in patients' clinical condition as reported by the physicians in the CGIC were observed as well as in the PROs (PGIC). The mean change from Baseline in the QOLIE-10-P total score increased steadily over time, indicating an improvement in health-related quality of life for patients. There was improvement for the TSQM-9, WPAI:GH, and NDDI-E, indicating improvement in patient perceived effectiveness, convenience, and global satisfaction with initiation of adjunctive brivaracetam treatment, improved patient activity and work impairment, better productivity, less work time missed, and improvements in depressive symptoms in patients contributing to these analyses. Per the modified SSQ, the proportion of patients reporting cognitive effects after seizures at Month 12 was low, and the overall frequency, severity, and bothersomeness of these cognitive effects of seizures were slightly reduced from Baseline. Overall seizure severity also improved.
- The safety profile was in line with the data of the SmPC and previously conducted real-world studies.
- Patients in subgroups with fewer lifetime AEDs, fewer concomitant AEDs, in earlier adjunctive treatment lines, and lower Baseline POS frequency showed numerically better effectiveness outcomes, as to be expected, compared to patients who were more refractory and in later adjunctive treatment lines.
- The results of this NIS showed that for patients with POS, brivaracetam added in earlier treatment lines was an effective and well tolerated therapy that supported improved quality of life, better clinical condition, work productivity, and overall satisfaction with the new therapy regime.

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15 APPENDICES

APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	N/A	24 Oct 2022	Protocol EP0103 Amendment 2.0
2	N/A	16 Oct 2023	Statistical Analysis Plan 2.0

APPENDIX 2. ADDITIONAL INFORMATION: NARRATIVES

Approval Signatures

Name: EP0103-study-report

Version: 1.0

Document Number: CLIN-000248878

Title: EP0103 - Study Report Body - NIS of BRV

Approved Date: 15 Oct 2024

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 14-Oct-2024 05:58:22 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 14-Oct-2024 09:48:01 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Subject Matter Expert Date of Signature: 15-Oct-2024 09:29:53 GMT+0000