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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Briviact

brivaracetam

Procedure no: EMEA/H/C/003898/P46/011

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	15 Aug 2022	15 Aug 2022	☐
☐	CHMP Rapporteur Assessment Report	19 Sept 2022	19 Sept 2022	☐
☐	CHMP members comments	03 Oct 2022	03 Oct 2022	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Oct 2022	n/a	☐
☒	CHMP adoption of conclusions:	13 Oct 2022	13 Oct 2022	☐

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LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ASM	antiseizure medication
BAE	behavioral adverse event
BRV	brivaracetam
CAE	cognitive adverse event
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
mFAS	Modified Full Analysis Set
min	minimum
NA	not applicable
PAE	psychiatric adverse event
POS	partial-onset seizure
PT	preferred term
RWE	real-world evidence
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	treatment-emergent adverse event
UAB	University of Alabama at Birmingham

1. Introduction

On July 25, 2022, the MAH submitted a completed paediatric study for Briviact, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that EP0159 is a pooled analysis of non-interventional, retrospective studies. This pooled analysis was not a pediatric analysis; however, the study included clinical chart review data for pediatric patients. Data from 1976 patients (5 countries and 9 cohorts) were made available. One cohort, SP4, was pediatric.

2.2. Information on the pharmaceutical formulation used in the study

EP0159 is a pooled analysis of non-interventional, retrospective, international studies that utilized clinical chart review cohorts of patients who initiated BRV in clinical practice. Eligible patients were treated with BRV according to standard clinical practice in their region. Pharmaceutical formulation was not specified as per study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- EPD332 and/or EP0159, in this report referred to as EP0159

Brivaracetam is a 2 pyrrolidone derivative and displays a high and selective interaction with synaptic vesicle protein 2A in the brain. This binding site appears to be the major target for its pharmacological activity.

In 2016, marketing authorization for the use of oral and intravenous BRV was granted as adjunctive treatment of partial-onset seizures (POS) with or without secondary generalization in adult and adolescent patients with epilepsy ≥16 years of age in the EU and US. An application for the extension of indication to the pediatric population from 4 years of age in the EU (adjunctive) and the US (adjunctive and monotherapy) based on the concept of extrapolation of efficacy data from the adult population was approved in 2018. On 24 Feb 2022, the extension of the indication for adjunctive treatment of POS in children aged from 2 years to 4 years (for all formulations) was approved in the EU.

2.3.2. Clinical study EP0159

EP0159 is a pooled analysis of non-interventional, retrospective, international studies that utilized clinical chart review cohorts of patients who initiated BRV in clinical practice. Eligible patients were treated with BRV according to standard clinical practice in their region. Eligible patients had at least 6 months and ideally 12 months of follow-up data after BRV initiation, until BRV discontinuation, loss to follow up, or death.

As this is a pooled analysis of BRV effectiveness and tolerability in clinical practice, there are no prespecified treatment groups.

The Patient Selection Period varied by country, as BRV approval, treatment guidelines, and reimbursement varied by country. The date of BRV product availability in each country marked the beginning of the Patient Selection Period. All patients had the ability to complete 12 months of follow up after BRV initiation (or at least 6 months of follow up in countries where BRV launch occurred after June 2018). The study period ended for each patient at the earliest date of the following events: BRV discontinuation, death, disenrollment, 365 days of follow up, and/or end of the study period. As such, patients were to have initiated BRV no earlier than Jan 2016 and no later than Dec 2019.

Of note, covariates in this study were routinely assessed upon initiation of clinical care for epilepsy. Although it was unlikely to have had prospectively collected records from birth for these variables, there was retrospective variable assessment at clinic entry, which was part of the medical record. When medical history data were not assessed, they were recorded as missing.

- Covariates assessed at Baseline included: age, sex, number of seizures per month, seizure types, concomitant ASMs, and comorbidities.
- Historical covariates included: age at epilepsy onset, duration of epilepsy, etiology, and previous ASMs.
- Censoring - Earliest of: Outcome of interest (BRV discontinuation), death, disenrollment, 365 days of follow up, or end of the study period.

CHMP´s comment

According to EP0159 Study report body, no measures were taken to impute or replace missing data. If there were patients with missing data, a missing row was added, and percentages were based on the number of patients in the analysis set (n).

Primary analysis was performed using data from the 3, 6 and 12 months timepoints by applying pragmatic intention to treat (p-ITT) rules as follows: If for a given timepoint, outcomes were missing due to end of follow up because BRV was discontinued during that timepoint, outcomes were assigned as follows for that timepoint and for the subsequent ones: seizure frequency: not applicable; seizure freedom at timepoint: no; seizure freedom from Baseline: no; and seizure reduction: non-responder.

This results in a conservative way to handle missing data for the below described endpoints ≥*50% seizure reduction from Baseline at 12 months* and *seizure freedom at 12 months*. Twenty-seven of the 66 patients (40.9%) in the pediatric SP4 cohort had discontinued before 12 months.

Cohorts of EP0159

Data from 1976 patients (5 countries and 9 cohorts) were made available to the EP0159 pooled analysis. The combined cohort used for the primary analysis (N=1644) of adult patients (defined in the protocol as ≥16 years of age) included cohorts SP1 (N=544), SP3 (N=196), GER (N=275), GER1 (N=213), AUS (N=291), and University of Alabama at Birmingham (UAB).

Pediatric patients

The EPD332/EP1059 pooled analysis was not a pediatric analysis; however, the study included clinical chart review data for pediatric patients. In the EP0159 real world evidence report (RWE) study report, all outcomes were investigated among the whole population; however, in order to reduce heterogeneity of the population, cohorts were split into adults (defined in the protocol as ≥16 years of age) and children (defined in the protocol as <16 years of age). The only pediatric cohort analyzed in the EP0159 RWE Study Report was the SP4 cohort, which included 66 pediatric patients (defined as <16 years of age per protocol).

All other cohorts (SP1, SP2, GER, GER1, AUS, UAB, and UK) were adult cohorts; however, data from an additional 9 pediatric patients (<16 years of age) from these cohorts were captured and excluded

from the adult cohorts (refer to EP1059 RWE Study Report Table 10 1). In addition, patients who were 16 and 17 years of age were considered adults per protocol (≥16 years of age) and were analyzed among the adult population; therefore, data from 11 patients (16 to 17 years of age) from these cohorts were captured. Due to the small pediatric sample size within each of these cohorts and because these 9 pediatric patients (<16 years of age) and 11 patients (16 to 17 years of age) did not constitute a homogenous subgroup of pediatric patients, data from these patients were not analyzed within the EP0159 RWE study report. Therefore, for these patients, no statistics were calculated, and they are only described as narratives in this assessment report.

CHMP's comment:

Cohort SP4 included 66 patients aged < 16 years. Five of the other cohorts had together included 9 patients aged <16 years of age, and two cohorts had included together 11 patients aged 16-17 years of age.

Objectives

The primary objective of this study was to evaluate the 12-month effectiveness and tolerability of BRV either on polytherapy or monotherapy in a large population of selected patients in routine clinical practice.

The secondary objective of this study was to describe 12-month BRV effectiveness and tolerability of BRV in specific patient subgroups.

Outcome measures

Primary outcome measures

- ≥50% seizure reduction from Baseline at 12 months (measured among only patients who have at least one seizure at baseline, the Modified Full Analysis Set (mFAS).
- BRV discontinuation due to BRV-related adverse events (AEs). Note: BRV discontinuations due to AEs were not collected in any cohort included in the pooled analysis; therefore, the posthoc tolerability outcome of BRV discontinuation due to tolerability was added.

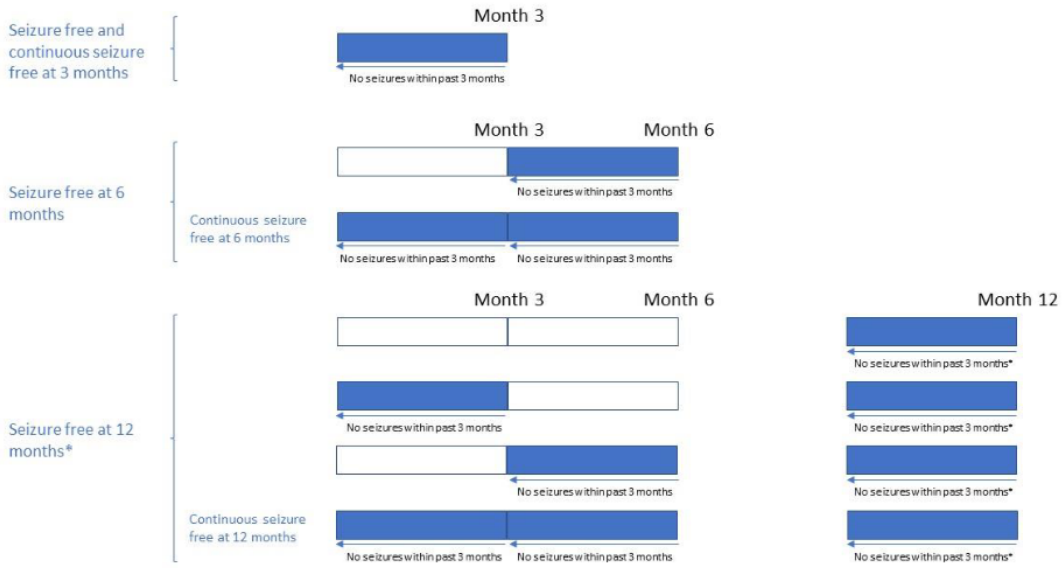
Secondary outcome measures

The following effectiveness outcome measures were assessed among all remaining patients on BRV at each timepoint:

- 3-, 6-month responder: ≥50% seizure reduction from Baseline (measured among only patients who had at least 1 seizure at Baseline [mFAS]).
- 3-, 6-, and 12-month seizure freedom. Note: Seizure freedom was defined as no seizures within 3 months prior to the timepoint, which differs from the SAP definition of seizure freedom (no seizures from BRV initiation); therefore, the posthoc effectiveness outcome below was added.
  - Posthoc effectiveness outcome: 3-, 6-, and 12-month continuous seizure freedom.*

  *The posthoc effectiveness outcome: 3-, 6-, and 12-month seizure freedom (defined as no seizures within 28 days prior to timepoint) was not measured and was replaced by the above posthoc effectiveness outcome of continuous seizure freedom.
- 3-, 6-, and 12-month retention rate: BRV discontinuation is the event. Patients having had no event (ie, did not discontinue BRV) are censored at end of follow up.
- Days of BRV exposure.

Figure 1: Definitions of seizure freedom and continuous seizure freedom after Baseline at 3, 6, and 12 months



*Assessed within past 3 months at minimum as some cohorts assessed seizure freedom since the previous visit.

The following tolerability and safety variables were analyzed:

- Incidence of AEs (AEs at 3, 6, and 12 months and at last visit were defined as since previous visit [not from BRV initiation]).*
- 3-, 6-, and 12-month severity (Medical Dictionary for Regulatory Activities [MedDRA] classification of AEs).
- 3-, 6-, and 12-month discontinuations due to AEs. Note: BRV discontinuations due to AEs were not collected in any cohort included in the pooled analysis; therefore, the posthoc tolerability outcome below was added.
  - Posthoc tolerability outcome: BRV discontinuation due to tolerability.
- Incidence of psychiatric AEs (PAEs) and nonPAEs**.
- Incidence of cognitive AEs (CAEs) and nonCAEs**.
- Incidence of behavioral AEs (BAEs) and nonBAEs**.

The following additional variables were analyzed:

- BRV dosing at 3, 6, and 12 months after BRV initiation and at last visit.
- Concomitant maintenance and rescue ASM (ie, AED) use (including dose of levetiracetam) at 3, 6, and 12 months after BRV initiation and at last visit.
- Concomitant prescriptions for other conditions (than epilepsy) at 3, 6, and 12 months after BRV initiation.

*At each visit, the number of AEs from the previous visit were reported and coded as Preferred Term (PT) using MedDRA version 24.0.

**AEs were classified by the UCB safety team into these categories: PAEs, CAEs and BAEs.

CHMP's comment:

It is questioned if it is purposeful to calculate 50% responders (and seizure freedom) in patients with the definition of at least 1 seizure at baseline. Some other minimum number of seizures at baseline may have been preferrable to obtain at least some accuracy in the calculations. According to table 15 (EP0159 tables), 2 patients were seizure free at index and 3 patients had 1-3 seizures per 28 days. Thus, the majority (61 patients) had ≥ 4 seizures per 28 days.

Efficacy – effectiveness

As efficacy was not assessed in the EP0159 RWE study report, only outcomes pertaining to effectiveness are presented.

Participants

The following pediatric data were captured in the EP0159 study:

- Data from 66 patients in the SP4 cohort (<16 years of age).
- Data from 9 patients (<16 years of age): data from these 9 patients will be described as narratives categorized by a number from 1 to 9 further down in this report.
- Data from 11 patients (16 to 17 years of age): data from these 11 patients will be described as narratives categorized by a letter from "A" to "K" in further down in this report.

Demographics

In the SP4 pediatric cohort, 12 patients (18.18%) were 0 to 5 years of age, 30 patients (45.45%) were 6 to 11 years of age, and 24 patients (36.36%) were 12 to 15 years of age. Forty-three patients (65.15%) were male, and 23 patients (34.85%) were female.

Of the 9 patients who were <16 years of age and who were excluded in the adult cohorts, 1 patient was 0 to 5 years of age, and 8 patients were 12 to 15 years of age. Five patients were male, and 4 patients were female.

Of the 11 patients who were 16 to 17 years of age, 5 patients were male, and 6 patients were female.

Baseline characteristics

In the SP4 pediatric cohort, the mean±standard deviation (SD) duration of epilepsy in 66 patients with observed data was 6.5±3.7 years (median [minimum (min), maximum (max)]: 6.0 years [1.0, 13.0]). For epilepsy etiology, most patients in the SP4 pediatric cohort had an unknown or other etiology (22 patients (33.33%); followed by 18 patients (27.27%) with a genetic etiology, 14 patients (21.21%) with a malformation of cortical development, 11 patients (16.67%) with a structural etiology (vascular, tumor-related, traumatic), and 1 patient (1.52%) with a metabolic disorder etiology. At Baseline, 27 patients (40.91%) had focal epilepsy, 22 patients (33.33%) had generalized epilepsy, and 17 patients (25.76%) had focal and generalized epilepsy, and a majority of patients (42 patients [63.64%]) had a seizure type of focal onset. Among patients with seizure subtype available, a majority of patients had unknown subtypes (56 patients [84.85%]). Of the 42 patients with focal onset seizures, 30 patients (71.43%) had focal seizures evolving to bilateral. Of the 25 patients with generalized seizures, 16 patients (64.00%) had myoclonic seizures and 18 patients (72.00%) had absence seizures. Two patients (3.03%) had seizure freedom at Baseline, and 64 patients (96.97%) did not have seizure freedom at Baseline. A majority of pediatric patients had a 28-day seizure frequency at index of ≥28 seizures, and the mean±SD 28 day seizure frequency at index for 66 patients with observed data was 186.7±394.1 seizures (median [min, max]:45.0 seizures [0.0, 2500.0]). Sixty-three patients (96.92%) used polytherapy at index and 2 patients (3.08%) used monotherapy at index. Of the 66

patients in the SP4 pediatric cohort, 64 patients (96.97%) had 12-month follow-up data for any variables.

For the 9 patients who were <16 years of age and who were excluded from the adult cohorts, disease, other Baseline, and treatment characteristics for each patient were as follows:

1. Patient 1 was 12 to 15 years of age at epilepsy onset and was documented as having an unknown or other etiology, generalized onset seizure type at Baseline, and unknown epilepsy type at Baseline. Their BRV dose at index was 100.0mg/day, and they used polytherapy (other concomitant ASM) at index. Their 28-day seizure frequency at index was >0 to <4 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.
2. Patient 2 was 6 to 11 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. Their 28 day seizure frequency at index was ≥28 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.
3. Patient 3 was 0 to 5 years of age at epilepsy onset and was documented as having a vascular etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. Their 28-day seizure frequency at index was ≥28 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.
4. Patient 4 was 6 to 11 years of age at epilepsy onset and was documented as having a malformation of cortical development etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose at index was 100.0mg/day, and they used polytherapy. Their 28-day seizure frequency at index was ≥28 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.
5. Patient 5 was 0 to 5 years of age at epilepsy onset and was documented as having a malformation of cortical development etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 25.0mg/day, and they used polytherapy. Their 28-day seizure frequency at index was 4 to <28 seizures, and they did not have seizure freedom at Baseline. They did not have 12 month follow-up data for any variables.
6. Patient 6 was 12 to 15 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 125.0mg/day, and they used polytherapy. Their 28 day seizure frequency at index was ≥28 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.
7. Patient 7 was 0 to 5 years of age at epilepsy onset and was documented as having a malformation of cortical development etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. Their 28 day seizure frequency at index was 4 to <28 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.
8. Patient 8 was 6 to 11 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 50.0mg/day, and they used polytherapy. Their 28 day

seizure frequency at index was 4 to <28 seizures, and they did not have seizure freedom at Baseline. They had 12 month follow-up data for any variables.

9. Patient 9 was 6 to 11 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and generalized epilepsy type at Baseline. At index, their BRV dose was 25.0mg/day, and they used monotherapy. Their 28 day seizure frequency at index was ≥28 seizures, and they were missing seizure freedom at Baseline. They did not have 12 month follow-up data for any variables.

For the 11 patients who were 16 to 17 years of age, disease, other Baseline, and treatment characteristics for each patient were as follows:

A. Patient A was 12 to 15 years of age at epilepsy onset and was documented as having an unknown or other etiology, generalized onset seizure type at Baseline, and generalized epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used monotherapy. They were missing 28 day seizure frequency at index and seizure freedom at Baseline. They did not have 12-month follow-up data for any variables.

B. Patient B was 6 to 11 years of age at epilepsy onset and was documented as having an unknown or other etiology, generalized onset seizure type at Baseline, and generalized epilepsy type at Baseline. At index, their BRV dose was 50.0mg/day, and they used polytherapy. They were missing 28 day seizure frequency at index and seizure freedom at Baseline. They did not have 12-month follow-up date for any variables.

C. Patient C was 12 to 15 years of age at epilepsy onset and was documented as having an unknown or other etiology, generalized onset seizure type at Baseline, and generalized epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used monotherapy. They were missing 28 day seizure frequency at index and seizure freedom at Baseline. They did not have 12-month follow-up data for any variables.

D. Patient D was 0 to 5 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 50.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

E. Patient E was 0 to 5 years of age at epilepsy onset and was documented as having an unknown or other etiology and focal onset seizure type at Baseline, and they were missing epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

F. Patient F was 6 to 11 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

G. Patient G was 0 to 5 years of age at epilepsy onset and was documented as having a malformation of cortical development etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 50.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

H. Patient H was 0 to 5 years of age at epilepsy onset and was documented as having a vascular etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

I. Patient I was 16 to 17 years of age at epilepsy onset and was documented as having an unknown or other etiology, generalized onset seizure type at Baseline, and generalized epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used monotherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

J. Patient J was 6 to 11 years of age at epilepsy onset and was documented as having a post infectious etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 100.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

K. Patient K was 0 to 5 years of age at epilepsy onset and was documented as having an unknown or other etiology, focal onset seizure type at Baseline, and focal epilepsy type at Baseline. At index, their BRV dose was 50.0mg/day, and they used polytherapy. They did not have data collected for 28 day seizure frequency at index, and they were missing seizure freedom at Baseline. They had 12-month follow-up data for any variables.

CHMP´s comment:

The indication of Briviact is focal onset seizures with or without bilateral spreading. Yet it is noted that one third of patients in cohort SP4 did not have focal seizures as recorded in the study, 1 of the 9 pediatric patients captured within the other cohorts did not have focal epilepsy and 4 of 11 among the 16–17-year-olds.

Effectiveness evaluation

Seizure reduction (≥50% from Baseline to 12 months)

Seizure reduction was assessed among patients who had at least 1 seizure at Baseline (mFAS).

In the SP4 pediatric cohort, 20 patients (31.25%) had seizure reduction ≥50% from Baseline to 12 months, and 44 patients (68.75%) did not have seizure reduction ≥50% from Baseline to 12 months. The mFAS for the SP4 pediatric cohort consisted of 64 patients who had ≥1 seizure recorded during Baseline.

Of the 9 patients who were <16 years of age and who were excluded from the adult cohorts, Patients 6, 7, and 8 had seizure reduction ≥50% from Baseline to 12 months; Patient 4 did not have seizure reduction ≥50% from Baseline to 12 months; and the remaining 5 patients were missing seizure reduction ≥50% from Baseline to 12 months:

All 11 patients who were 16 to 17 years of age did not have data collected for seizure reduction ≥50% from Baseline to 12 months.

CHMP´s comment:

Studies in adults (doses 50-200mg) have shown 50% responder rates between 22.0 and 38.9%. In this pediatric cohort the 50% responder rate at 12 months was 31.3% which is within the interval found in studies in adults.

Seizure freedom (12 months)

In the SP4 pediatric cohort, seizure freedom after Baseline occurred in 10 patients (15.15%) at 12 months.

Of the 9 patients who were <16 years of age and who were excluded from the adult cohorts, Patient 7 had seizure freedom after Baseline at 12 months; Patients 4, 6, and 8 did not have seizure freedom after Baseline at 12 months; and Patients 1, 2, 3, 5, and 9 were missing seizure freedom after Baseline at 12 months.

Of the patients who were 16 to 17 years of age, Patients F and I had seizure freedom after Baseline to 12 months; Patients D, E, G, H, and K did not have seizure freedom after Baseline to 12 months; Patient J was missing seizure freedom after Baseline to 12 months; and Patients A, B, and C did not have data collected for seizure freedom after Baseline to 12 months.

CHMP´s comment:

Seizure freedom at 12 months was defined as seizure free the last three months. In the pivotal studies in adults, seizure freedom was recorded when there was continuous seizure freedom for the whole 12 weeks study period. Thus, the duration of the seizure free interval is the same, but the time from treatment onset differs. In cohort SP4, 15,2% of patients were seizure free at 12 months which is a larger proportion of patients reaching seizure freedom compared to the adult pivotal studies: 2,5 % (4/161), 5,1 % (17/332) and 4,0 % (10/249) of patients who received brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively. Of placebo treated patients 0,5 % (2/418) were classified as seizure free.

Effectiveness conclusion by the Applicant

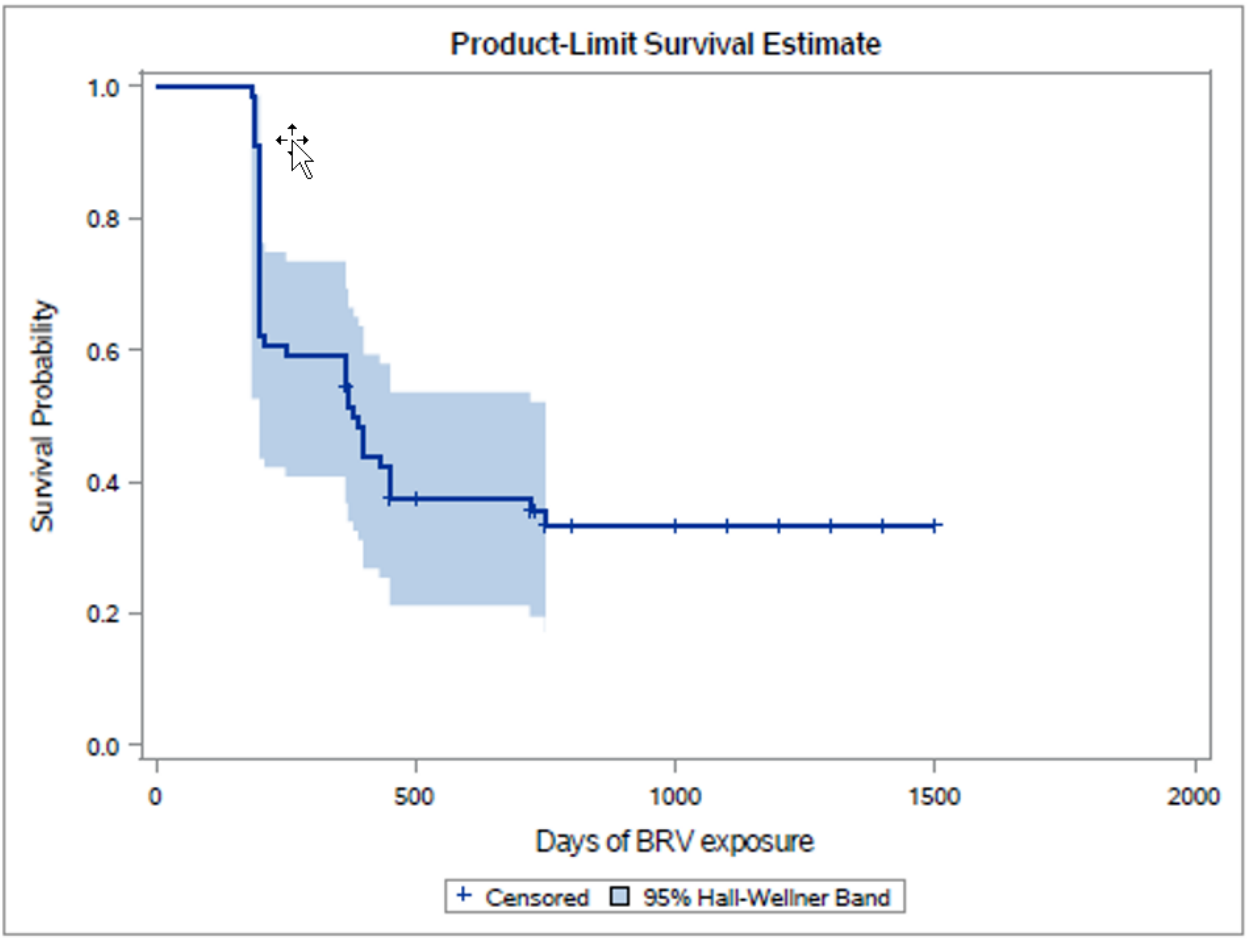
The results of the EP0159 study are in line with the recently published studies of BRV. The effectiveness results indicate a positive benefit-risk balance of BRV.

Safety

In the SP4 pediatric cohort, 43 patients (65.15%) discontinued BRV, and 23 patients did not discontinue BRV. The 43 patients who discontinued BRV were missing discontinuation reason; therefore, the patients who discontinued BRV due to tolerability were not collected at any timepoint for the SP4 pediatric cohort.

A Kaplan-Meier curve for treatment retention where BRV discontinuation is the event is presented for the SP4 cohort (Figure 2). Patients having had no event (ie, did not discontinue BRV) were censored at end of follow up. After 380 days, less than 50% of the population will remain on BRV.

Figure 2: Kaplan-Meier curve for treatment retention for the SP4 pediatric cohort



BRV=brivaracetam; SP=Spain
Note: After 380 days (product-limit median), less than 50% of the population will remain on BRV.
Source: EP0159 RWE Study Report Figure 2-01

Of the 9 patients who were <16 years of age and who were excluded from the adult cohorts, Patient 3 discontinued BRV for the reason of tolerability, Patient 4 discontinued BRV for the reason of other, Patient 8 discontinued BRV for the reason of effectiveness and tolerability, and the remaining 6 patients did not discontinue BRV.

Of the 11 patients who were 16 to 17 years of age, Patient H discontinued BRV for the reason of tolerability, Patient K discontinued BRV for the reason of effectiveness and tolerability, and the remaining 9 patients did not discontinue BRV.

CHMP´s comment

Of the 66 pediatric patients, 43 (65.2) discontinued. Twenty-seven (40.9%) had discontinued before 12 months. Median days of exposure was 375 and mean time of exposure was 484 days. There is no information regarding the causes for discontinuation and it is not possible to analyse e g proportions of patients who discontinues due to lack of efficacy or tolerability issues/AEs.

Adverse events

The percentages were calculated among all pediatric patients with a documented observation of having a TEAE or not having a TEAE. As such, patients with missing data and patients with data not collected were excluded from the calculation.

In the SP4 pediatric cohort, treatment-emergent adverse events (TEAEs) were documented for 12 patients (18.18%) since previous visit at 3 months, 10 patients (15.15%) since previous visit at 6 months, 3 patients (4.84%) since previous visit at 12 months, and 12 patients (18.18%) since previous visit at last visit.

In the SP4 pediatric cohort, the incidence of TEAEs by PT documented since previous visit included the following:

- At 3 months: irritability and hypersomnia (5 patients [7.58%], each), insomnia (3 patients [4.55%]), and dizziness (1 patient [1.52%]).
- At 6 months and 12 months: AEs were documented for 10 patients (15.15%) and 3 patients (4.84%), respectively; however, these AEs were not further described in the database.
- At last visit: irritability and hypersomnia (5 patients [7.58%], each), insomnia (3 patients [4.55%]), and dizziness (1 patient [1.52%]).

In the SP4 pediatric cohort, most TEAEs were moderate at 3 months (8 patients [80.00%]) and 6 months (6 patients [66.67%]). At 12 months and last visit, 1 patient was documented at each timepoint as having mild TEAEs. At 3 months and 12 months, no severe TEAEs were documented, and at 6 months a severe TEAE was documented for 1 patient (11.11%). No life-threatening TEAEs were documented at any timepoint.

Discontinuations due to AEs were not collected in the participating cohorts; alternatively, discontinuations due to tolerability were assessed.

In the SP4 pediatric cohort, no PAEs, CAEs, or BAEs were documented at 3 months or at last visit. At 6 months and 12 months, the AEs that occurred were not further described in the database.

CHMP´s comment:

The reported AEs in SP4 are known ADRs of brivaracetam and already listed in the SmPC of Briviact section 4.8. The frequencies of the AEs reported in SP4 are in line with those tabulated in 4.8.

One patient reported a severe AE at the 6 months visit. There is no additional information regarding the type of AE, the outcome of possible causality.

It is stated that discontinuations due to AEs were not collected in the participating cohorts; alternatively, discontinuations due to tolerability were assessed. However, no such data are available either and the reasons for discontinuation is unknown.

For the 9 patients who were <16 years of age and who were excluded from adult cohorts, the incidence of TEAEs, TEAEs by PT (as applicable), and TEAE severity (as applicable) documented for each patient since previous visit at 3, 6, and 12 months and at last visit were as follows:

1. Patient 1 had no TEAEs at 3, 6, or 12 months or at last visit.
2. Patient 2 had TEAEs at 3 months (aggression; mild in severity), 6 months (AE occurred by not further described in the database), and last visit (AE occurred by not further described in the database). No TEAEs were reported at 12 months.

3. Patient 3 had TEAEs at 3 months (decreased appetite and fatigue; severe in severity) and last visit (AE occurred by not further described in the database). No TEAEs were reported at 6 or 12 months.
4. Patient 4 had no TEAEs at 3, 6, or 12 months or at last visit.
5. Patient 5 was missing incidence of TEAEs at 3, 6, and 12 months and at last visit because they had no visit at any timepoint.
6. Patient 6 had TEAEs at 6 months (bradyphrenia and memory impairment; mild in severity) and at last visit (no TEAE description; mild in severity). No TEAEs were reported at 3 months or 12 months.
7. Patient 7 had TEAEs at 3 months (irritability and somnolence; mild in severity), 6 months (irritability; mild in severity), and at last visit (no TEAE description; mild in severity). No TEAEs were reported at 12 months.
8. Patient 8 had TEAEs at 6 months (bradyphrenia and memory impairment; moderate in severity), 12 months (bradyphrenia and memory impairment; moderate in severity), and at last visit (no TEAE description; moderate in severity). No TEAEs were reported at 3 months.
9. Patient 9 had no TEAEs at 3 or 6 months or at last visit and was missing incidence of TEAEs at 12 months because they had no visit at the timepoint.

For the 11 patients who were 16 to 17 years of age, the incidence of TEAEs, TEAEs by PT (as applicable), and TEAE severity (as applicable) documented for each patient since previous visit at 3, 6, and 12 months and at last visit were as follows:

A. Patient A did not have TEAE data collected at 3, 6, or 12 months and had no TEAEs at last visit.
B. Patient B did not have TEAE data collected at 3, 6, or 12 months and had no TEAEs at last visit.
C. Patient C did not have TEAE data collected at 3, 6, or 12 months and had no TEAEs at last visit.
D. Patient D had no TEAEs at 3, 6, or 12 months or at last visit.
E. Patient E had TEAEs at 12 months (somnolence; moderate in severity) and at last visit (no TEAE description; moderate in severity). No TEAEs were reported at 3 or 6 months.
F. Patient F had TEAEs at 3 months (coordination abnormal and dizziness; moderate in severity). No TEAEs were reported at 6 or 12 months or at last visit.
G. Patient G had TEAEs at 3 months (irritability and anxiety; moderate in severity), 6 months (irritability and anxiety; moderate in severity), and at last visit (AE occurred but not further described in the database). No TEAEs were reported at 12 months.
H. Patient H had TEAEs at 3 months (NA [being evil, contains, prostration, skin problems or other; terms were reported as a sole AE and did not present with a PT to code the AE adequately]; severe in severity), 6 months (NA [being evil, contains, prostration, skin problems or other]; severity not described), and at last visit (no TEAE description; severe in severity). They were missing incidence of TEAEs at 12 months because they had no visit at the timepoint.
I. Patient I had no TEAEs at 3, 6, or 12 months or at last visit.
J. Patient J had no TEAEs at 3, 6, or 12 months or at last visit.
K. Patient K had TEAEs at 3 months (coordination abnormal and dizziness; severe in severity), and at last visit (AE occurred but not further described in the database). They were missing incidence of TEAEs at 6 and 12 months because they had no visit at the timepoints.

CHMP´s comment:

Among the 20 patients < 18 years old who were included in other cohorts than SP4, 2 patients reported bradyphrenia and memory impairment (mild and moderate intensity respectively). These are not established ADRs of brivaracetam, but memory impairment was one of the most frequently reported PTs in adults during the last PSUR period (EMEA/H/C/PSUSA/00010447/202101). Memory impairment was also reported after medication error and overdose.

Bradyphrenia and memory impairment reflect mild cognitive impairment, a common problem among anti-epileptic medications as a group (Sung-Pa *et al*, J Clin Neurol, 2008). However, brivaracetam has been associated with a smaller such risk than many other ASMs (Sarkis *et al*, J Neurol, 2018). A proportion of patients with epilepsy also suffer from (mild) cognitive impairment. As no narratives are presented, it is not possible to assess causality in the current two cases. However, the MAH should commit to provide a cumulative review regarding cognitive impairment in brivaracetam treatment in the next PSUR.

Two other patients reported abnormal coordination, moderate and severe intensity respectively. Impaired coordination is not listed as an ADR of brivaracetam but is reported to occur by a frequency of uncommon for levetiracetam. As narratives as lacking, causality cannot be assessed in the current two cases. As impaired coordination may be a class effect, the MAH should provide a cumulative review regarding impaired coordination in brivaracetam treatment in the next PSUR.

Safety conclusions by the applicant

The results of the EP0159 study are in line with the recently published studies of BRV and no evidence of new safety concerns was found.

Benefits and risks conclusions by the Applicant

The results of the EP0159 study are in line with the recently published studies of BRV. The effectiveness results indicate a positive benefit-risk balance of BRV. It provides additional evidence that BRV as prescribed in the real world is effective and well-tolerated among children and adolescents.

The results of EP0159 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). No changes to the approved EU Product Information for Briviact are being proposed with this submission based on EP0159 results.

2.3.3. Discussion on clinical aspects

The SP4 cohort of study EP0159 consisted of 66 paediatric patients. Additional data were gathered from paediatric patients (<16 years old) and 16-17-year-olds included in other cohorts (N=9 and N=11 respectively).

The primary outcome measure was responder rate at 12 months (at least 50% seizure reduction month 9-12 compared to baseline). The responder rate was 31.3% in the SP4 cohort. Studies in adults (doses 50-200mg) have shown 50% responder rates between 22.0 and 38.9%, and thus the PS4 responder rate is within the interval found in the pivotal studies in adults.

15.2% of paediatric patients in SP4 were seizure free at 12 months which can be compared to seizure freedom achieved in the adult pivotal studies: 2.5 % (4/161), 5.1 % (17/332) and 4.0 % (10/249) of patients who received brivaracetam 50 mg/day, 100 mg/day and 200 mg/day respectively.

The pivotal studies in adults and EP0159 differ in many ways which may explain some of the difference in efficacy/effectiveness, but the postmarketing data obtained in EP0159 do not give rise to any concern regarding effectiveness.

Most of the reported TEAS are ADRs already known and listed for brivaracetam. Some reports of TEAE did not include any PT, including one of severe intensity.

Among the 20 patients < 18 years old who were included in other cohorts than SP4, 2 patients reported bradyphrenia and memory impairment (mild and moderate intensity respectively). These are not established ADRs of brivaracetam, but memory impairment was one of the most frequently reported PTs in adults during the last PSUR period (EMEA/H/C/PSUSA/00010447/202101). Memory impairment was also reported after medication error and overdose.

Bradyphrenia and memory impairment reflect mild cognitive impairment, a common problem among anti-seizure medications as a group (Sung-Pa et al, J Clin Neurol, 2008). However, brivaracetam has been associated with a smaller such risk than many other ASMs (Sarkis et al, J Neurol, 2018). A proportion of patients with epilepsy also suffer from (mild) cognitive impairment. As no narratives are presented, it is not possible to assess causality in the current two cases. However, the MAH should provide a cumulative review (company safety database, Eudravigilance, and literature) regarding cognitive impairment in brivaracetam treatment in the next PSUR.

Two other patients reported abnormal coordination of moderate and severe intensity, respectively. Impaired coordination is not listed as an ADR of brivaracetam but is reported to occur by a frequency of uncommon for levetiracetam. As narratives as lacking, causality cannot be assessed in the current two cases. Impaired coordination might be a class effect and the MAH should provide a cumulative review (company safety database, Eudravigilance, and literature) regarding impaired coordination in brivaracetam treatment in the next PSUR.

Discontinuations due to AEs were not collected in the participating cohorts and it is stated that alternatively, discontinuations due to tolerability were assessed. However, no such data are available and the reasons for discontinuations are unknown.

No safety concern that warrants regulatory action has been identified.

3. Rapporteur's overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required, however the MAH should submit cumulative reviews regarding cognitive dysfunction (including memory impairment), and impaired coordination within the next PSUR.