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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/P46/012

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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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	26 Dec 2022	26 Dec 2022	☐
☐	CHMP Rapporteur Assessment Report	30 Jan 2023	30 Jan 2023	☐
☐	CHMP members comments	13 Feb 2023	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Feb 2023	n/a	☐
☒	CHMP adoption of conclusions:	23 Feb 2023	23 Feb 2023	☐

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1. Introduction

BRIVIACT is currently approved in the EU for use as adjunctive therapy in the treatment of partial onset seizures (POS) with or without secondary generalization in adults, adolescents, and children ≥2 years of age with epilepsy.

On 8 December 2022, the MAH submitted a completed paediatric study for brivaracetam (Briviact), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of a post-authorisation measure.

A short critical expert overview has also been provided.

The MAH is of the opinion that no change is deemed necessary to the Briviact Product Information in view of the data submitted in this application.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that the study title and the number is: "A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Evaluate the Efficacy and Safety of Adjunctive Brivaracetam in Subjects (≥16 to 80 Years of Age) with Partial Seizures with or without Secondary Generalization, **EP0083**.

2.2. Information on the pharmaceutical formulation used in the study

T Brivaracetam was supplied as oral film-coated tablets of BRV 25mg and BRV 50mg.

2.3. Clinical aspects

2.3.1. Introduction

The MAH is providing a report of the final results of EP0083. EP0083 was a randomized, double-blind, placebo-controlled, multicenter study evaluating the efficacy of 2 doses of brivaracetam (50mg/day and 200mg/day) compared with placebo as adjunctive treatment in study participants (≥16 to 80 years of age) with partial seizures with or without secondary generalization despite current treatment with 1 or 2 concomitant antiepileptic drugs. Safety and tolerability were also evaluated. Participants completed an 8-week prospective Baseline Period, followed by a 12-week Treatment Period. After the Treatment Period, participants had the option to continue brivaracetam treatment in EP0085.

Of a total of 449 randomized participants, 425 participants (94.7%) completed the study. Of these 425 participants, 20 were <18 years of age at the start of the study: 6 in the placebo group 14 in the BRV treatment groups. A total of 13 participants in the BRV treatment groups completed the study.

2.3.2. Clinical study

EP0083: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Evaluate the Efficacy and Safety of Adjunctive Brivaracetam in Subjects (≥16 to 80 Years of Age) with Partial Seizures with or without Secondary Generalization.

Methods

Study participants

This was a multicenter study that included 94 enrolling sites in 7 countries.

To be eligible to participate in this study, participants must have been between 16 to 80 years of age at Visit 1 with a well-characterized focal epilepsy/epileptic syndrome according to the 1989 International League Against Epilepsy (ILAE) classification.

Participants must have had an electroencephalogram reading compatible with the clinical diagnosis of focal epilepsy within the last 5 years and a brain magnetic resonance imaging/computed tomography scan performed within the last 2 years.

Participants must have had at least 8 partial seizures during the 8-week Baseline Period with at least 2 partial seizures during each 4-week interval of the Baseline Period, and at least 2 partial seizures, whether or not secondary generalization, per month during the 3 months preceding Visit 1.

Additionally, the participant's condition must have been uncontrolled while treated by 1 or 2 permitted concomitant AED(s).

Participants were not eligible if they had experienced simple partial seizure nonmotor as the only seizure type, had exclusively experienced febrile seizures, or were being concurrently treated with LEV (or had taken LEV within 90 days prior to Visit 1).

Participants were also not eligible if their seizures could not be reliably counted on a regular basis due to their fast and repetitive occurrence (clusters or flurries) or they had a history or presence of status epilepticus during the year preceding Visit 1 or during Baseline.

Participants who had prior LEV use were enrolled during the study in such a way that a maximum of 30% of prior LEV users in the study population was preserved over the duration of the study.

Treatments

The total duration of the study per study participant was 26 weeks with a maximum 16-weeks exposure to BRV consisting of the following study periods:

- Baseline Period (8 weeks)
- Treatment Period (12 weeks)
- Down-Titration Period (4 weeks)
- Study Drug-Free Period (2 weeks)
- Transition Period (2 weeks) (required for participants participating in the LTFU study [EP0085] or MAP);

Some participants were eligible for conversion to a long-term follow-up (LTFU) study (EP0085) or managed access program (MAP) upon completion of the Treatment Period and a 2-week Transition Period. In order to ensure uninterrupted treatment, BRV was provided to study participants who would be entering into the MAP in an open-label temporary study period. If BRV was commercially available upon completion of the Treatment Period and T Transition Period, the participants received BRV directly without entering the LTFU study (EP0085) or MAP.

The 4-week Down-Titration Period followed by a 2-week Study Drug-Free Period served participants not entering the LTFU study (EP0085) or MAP.

Objective(s)

The primary objective was to evaluate the efficacy of BRV compared with placebo (PBO) as adjunctive treatment in study participants (≥16 years to 80 years of age) with partial seizures with or without secondary generalization despite current treatment with 1 or 2 concomitant antiepileptic drugs (AEDs).

The secondary objective was to assess the safety and tolerability of BRV in study participants ≥16 years to 80 years of age.

Outcomes/endpoints

Efficacy

The **primary efficacy variable** was the partial seizure frequency per 28 days during the 12-week Treatment Period.

Secondary efficacy variables were as follows:

- The 50% responder rate based on percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period
- Percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period
- Categorized percent reduction in partial seizure frequency per 28 days from Baseline to the 12-week Treatment Period
- All seizure frequency (partial, generalized, and unclassified epileptic seizures) per 28 days during the 12-week Treatment Period. Due to the few participants <18 years of age in each treatment group (6, 9, and 4 participants in the PBO, BRV 50mg/day, and BRV 200mg/day groups, respectively) this analysis was not possible. There were no participants with generalized seizure and only 1 participant with unclassified seizure at Baseline (Table 4.5.P); therefore, the seizure frequency results for all seizures would have been nearly the same as the results for partial seizures.
- Seizure freedom (partial, all epileptic seizure) during the 12-week Treatment Period
- Time to nth (n=1, 5, 10) partial seizure during the 12-week Treatment Period. Due to the few participants <18 years of age in each treatment group (6, 9, and 4 participants in the PBO, BRV 50mg/day, and BRV 200mg/day groups, respectively), the data would have been too sparse for a Kaplan-Meier analysis for this endpoint.

Safety

The **primary safety variables** were:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of TEAEs leading to study withdrawal
- Incidence of treatment-emergent serious adverse events (SAEs)
- The other safety variables were:
- Changes in clinical laboratory tests parameters (blood chemistry [biochemistry], hematology, urinalysis)
- Electrocardiogram (ECG) parameters and findings

- Changes in vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], and pulse rate)
- Changes in body weight
- Physical examination
- Neurological examination
- Mental status
- Psychiatric status

The safety variable during the open-label temporary period was the incidence of TEAEs, as reported spontaneously by the study participant or observed during the temporary period for providing BRV.

Sample size

A total of 569 study participants between 16 to 80 years were screened and there were 122 screen failures. Of the 449 randomized participants, 425 participants (94.7%) completed the study.

Overall, 20 participants <18 years of age started the study: 6 in the PBO group, 10 in the BRV 50mg/day group, and 4 in the BRV 200mg/day group. A total of 17 participants (85.0%) completed the study and 3 participants (15.0%) discontinued the study: 2 participants (33.3%) in the PBO group (due to adverse event [AE] and lost to follow up) and 1 participant (10.0%) in the BRV 50mg/day group (due to "other") (Table 2–1).

Of the 20 participants who started the Treatment Period, 18 participants (90.0%) completed the Treatment Period and 17 of these completers (85.0%) entered and completed the Transition Period. Neither of the 2 study participants who discontinued the Treatment Period entered the Down-Titration Period.

Disposition and discontinuation for study participants <18 years of age comprising the RS during the Double-blind Period, is summarized in Table 2–1.

Table 2–1: Disposition and discontinuation reasons (<18 years of age [RS])

	PBO N=6 n (%)	BRV 50mg/day N=10 n (%)	BRV 200mg/day N=4 n (%)	BRV all N=14 n (%)	All participants N=20 n (%)
Started study	6 (100)	10 (100)	4 (100)	14 (100)	20 (100)
Completed study	4 (66.7)	9 (90.0)	4 (100)	13 (92.9)	17 (85.0)
Discontinued study	2 (33.3)	1 (10.0)	0	1 (7.1)	3 (15.0)
Reason for discontinuation					
Adverse event	1 (16.7)	0	0	0	1 (5.0)
Lack of efficacy	0	0	0	0	0
Protocol violation	0	0	0	0	0
Lost to follow up	1 (16.7)	0	0	0	1 (5.0)
Withdrawal by participant	0	0	0	0	0
Other	0	1 (10.0)	0	1 (7.1)	1 (5.0)
Started Treatment Period	6 (100)	10 (100)	4 (100)	14 (100)	20 (100)
Completed Treatment Period	5 (83.3)[a]	9 (90.0)	4 (100)	13 (92.9)	18 (90.0)
Discontinued Treatment Period	1 (16.7)	1 (10.0)	0	1 (7.1)	2 (10.0)
Reason for discontinuation					
Adverse event	1 (16.7)	0	0	0	1 (5.0)
Lack of efficacy	0	0	0	0	0
Protocol violation	0	0	0	0	0
Lost to follow up	0	0	0	0	0
Withdrawal by participant	0	0	0	0	0
Other	0	1 (10.0)	0	1 (7.1)	1 (5.0)

BRV=brivaracetam; PBO=placebo; RS=Randomized Set

Note: A study participant was considered completing the study if this participant completed the full extent of the double-blind part of the study (Treatment Period and the Down-Titration Period plus Study Drug-Free Period or the Transition Period).

Note: A participant was considered completing the Down-Titration Period if this participant also completed the Study Drug-Free Period.

Note: A participant was considered completing the Transition Period if this participant transitioned to Long Term Follow-Up or Managed Access Program.

[a] One participant finished the Treatment Period but did not enter the Down-Titration Period or the Transition Period.

Data source: Table 1.4.1.P

Randomisation and blinding (masking)

The study was randomized and double blind.

Results

Recruitment

First study participant enrolled: 22 Aug 2017. Last study participant completed: 30 June 2022

Baseline data

Overall, the mean age of participants comprising this paediatric subset was 16.5 years (range: 16 to 17 years) and half of the participants (10 participants [52.6%]) were in the <17 years age category. The mean age of participants in the PBO group was 16.8 years; the mean age of participants in BRV treatment groups was 16.3 years.

All 19 study participants <18 years of age were Asian and the majority (18 participants [94.7%]) were not of Hispanic or Latino ethnicity.

Overall, the mean duration of epilepsy for participants at Baseline was 9.03 years (range: 0.4 to 16.5 years), and the mean age at onset of the first seizure was 7.90 years (range: 0.2 to 16.7 years), both of which were similar for the BRV 50mg/day and 200mg/day treatment groups; however, the mean duration of epilepsy was shorter in the PBO group (6.93 years vs 9.79 and 10.48 years for the BRV 50mg/day and 200mg/day treatment groups, respectively) and the mean age at time of first seizure was older in the PBO group (10.24 years vs 7.15 and 6.08 years for the BRV 50mg/day and 200mg/day treatment groups, respectively).

All 19 participants exhibited localization related epileptic syndrome, with the majority (13 participants [68.4%]) in the symptomatic category, a trend which was consistent with the placebo and BRV 50mg/day treatment groups; however, in the BRV 200mg/day group, 2 of the 4 participants (50.0%) were in the cryptogenic category. Overall, 3 participants (15.8%) had epileptic syndrome further classified as generalized, all of which were idiopathic. All participants had POS, as required by the inclusion criteria for this study.

Some participants had more than 1 type of POS seizure: overall, 12 participants (63.2%) experienced complex partial seizures, and 9 participants each (47.4% each) experienced partial evolving to secondary generalized seizures and simple partial. Of those who experienced simple partial seizures, the majority (8 participants [42.1%]) exhibited motor symptoms. Two participants (10.5%) also experienced generalized seizures.

All 19 participants <18 years of age were taking at least 1 AED at study entry, most commonly valproate (7 participants [36.8%]), carbamazepine (6 participants [31.6%]), and phenobarbital (4 study participants [21.1%]). There were no notable differences between the PBO and BRV all groups.

Efficacy results

The MAH provided descriptive summary tables for the subset of participants <18 years of age:

- The primary efficacy variable was the partial seizure frequency per 28 days during the 12-week Treatment Period. The percent reduction in the 28-day adjusted POS frequency over PBO was 35.2% and 59.8% in the BRV 50mg/day and BRV 200mg/day groups, respectively (Table 2-2).

- For the key secondary efficacy endpoint, the 50% responder rate for POS frequency in the PBO group was lower (16.7%) compared with the BRV 50mg/day group and the BRV 200mg/day group (44.4% and 75.0%, respectively), (Table 2-3).
- For another key secondary efficacy endpoint, the median percent reduction in POS frequency from Baseline to the Treatment Period was lower in the PBO group (12.2%) compared with the BRV 50mg/day and BRV 200mg/day groups (49.5% and 68.3%, respectively) (Table 2-4).
- For categorized reductions in POS frequency from Baseline, larger proportions of participants in the BRV 50mg/day and BRV 200mg/day groups showed 75% to <100%, 50% to 75%, and 25% to <50% reductions compared with the PBO group (Table 2-5).
- All participants in the BRV treatment groups and 5 participants (83.3%) in the PBO group completed the Treatment Period; no participant achieved seizure freedom (from all seizures or from POS) during the Treatment Period.

Table 2–2: Overall percent reduction over PBO in the 28-day adjusted POS frequency (<18 years of age [FAS])

Statistics	PBO N=6	BRV 50mg/day N=9	BRV 200mg/day N=4
Number of participants analyzed	6	9	4
Back-transformed LS means	12.8	7.9	4.6
Percent reduction over PBO		35.2	59.8

BRV=brivaracetam; FAS=full analysis set; LS=least squares; PBO=placebo; POS=partial onset seizure
Note: Effect estimates and treatment group comparisons are based on analysis of covariance with log-transformed [log(x+1)].Treatment Period 28-day adjusted POS frequency as the outcome and an effect for treatment and log-transformed 28-day adjusted Baseline partial onset seizure frequency as a continuous covariate.
Data Source: Table 7.2.1.P

Table 2–3: 50% responder rate for POS frequency (<18 years of age [FAS])

	PBO N=6	BRV 50mg/day N=9	BRV 200mg/day N=4
Number of participants analyzed	6	9	4
Responders, n (%)	1 (16.7)	4 (44.4)	3 (75.0)
95% CI of the responder rate	0.4, 64.1	13.7, 78.8	19.4, 99.4

BRV=brivaracetam; CI=confidence interval; FAS=Full Analysis Set; PBO=placebo; POS=partial onset seizure;
Note: 95% CI of the responder for each treatment group was based on an exact method for the binomial distribution (Clopper-Pearson).
Data Source: Table 7.4.1.P

Table 2–3: Percent reduction in POS frequency from Baseline (FAS)

	PBO N=6	BRV 50mg/day N=9	BRV 200mg/day N=4
Statistic			
n	6	9	4
Mean (SD)	12.3 (32.7)	34.9 (47.8)	66.8 (20.3)
Median (min, max)	12.2 (-33, 65)	49.5 (-47, 83)	68.3 (42, 89)
Median difference vs PBO		35.4	56.1
95% CI [LL, UL]		-40.7, 73.5	-4.7, 109.8

BRV=brivaracetam; CI=confidence interval; FAS=Full Analysis Set; LL=lower limit; Max=maximum; Min=minimum; PBO=placebo; POS=partial onset seizure; SD=standard deviation; UL=upper limit
Note: Hodges Lehmann nonparametric effect estimates and corresponding 2-sided 95% CIs are provided for the effect difference between each BRV treatment group and placebo.
Data Source: Table 7.6.1.P

Table 2–4: Overall categorized percent reduction in POS frequency from Baseline to the Treatment Period (<18 years of age [FAS])

	PBO N=6	BRV 50mg/day N=9	BRV 200mg/day N=4
Number of participants analyzed	6	9	4
Category, n (%)			
100%	0	0	0
75% to <100%	0	1 (11.1)	2 (50.0)
50% to <75%	1 (16.7)	3 (33.3)	1 (25.0)
25% to <50%	0	2 (22.2)	1 (25.0)
-25% to <25%	4 (66.7)	1 (11.1)	0
<-25%	1 (16.7)	2 (22.2)	0

BRV=brivaracetam, FAS=Full Analysis Set; PBO=placebo; POS=partial onset seizure
Data Source: Table 7.7.P

Safety results

- Overall, 3 study participants (50.0%) in the PBO group and 8 participants (61.5%) in the BRV all group reported at least 1 TEAE (Table 2-5). One participant each (16.7% each) in the PBO group reported TEAEs that led to discontinuation and permanent withdrawal of IMP. Overall, 1 participant (16.7%) in the PBO group and 6 participants (46.2%) in the BRV all group reported TEAEs considered by the Investigator to be related to the IMP (Table 2-6).
- There were no serious TEAEs, severe TEAEs, TEAEs requiring a dose change, or deaths in participants <18 years of age during the study.
- In the BRV all group, the most commonly reported TEAEs were somnolence and weight decreased (each 3 participants [23.1%]), followed by pyrexia, malaise, and sinus arrhythmia (each 2 participants [15.4%]); all other PTs were reported by 1 participant each. In the PBO group, each PT was only reported by 1 study participant.
- The majority of TEAEs were mild in intensity.
- In the PBO group, 1 participant (16.7%) reported a total of 3 TEAEs (GGT increased, ALT increased, and weight increased) that were considered related to IMP by the Investigator. In the BRV all group, 6 participants (46.2%) reported a total of 13 TEAEs considered related to IMP by the Investigator, most commonly somnolence (3 participants [23.1%]) in the BRV all group. All other TEAEs considered related to IMP by the Investigator were reported by no more than 1 study participant in either BRV treatment group.
- One participant in the PBO group reported TEAEs of ocular hyperemia and epilepsy that led to permanent discontinuation of IMP and the study; there were no discontinuations in the BRV treatment groups.
- No clinically relevant differences between treatment groups were observed for any changes from Baseline in hematology, biochemistry, urinalysis, vital signs, or ECGs. No potential drug-induced liver injury events were reported during the study. No safety signals were identified.

Table 2–5: Overview - Incidence of TEAEs (<18 years of age [SS])

Category	PBO N=6 n (%) [#]	BRV 50mg/day N=9 n (%) [#]	BRV 200mg/day N=4 n (%)[#]	BRV all N=13 n (%)[#]
Any TEAEs	3 (50.0) [7]	5 (55.6) [23]	3 (75.0) [18]	8 (61.5) [41]
Serious TEAEs	0	0	0	0
Study participant discontinuations due to TEAEs	1 (16.7) [2]	0	0	0
Permanent withdrawal of IMP due to TEAEs	1 (16.7) [2]	0	0	0
TEAEs requiring dose change	0	0	0	0
IMP-related TEAEs	1 (16.7) [3]	3 (33.3) [6]	3 (75.0) [7]	6 (46.2) [13]
Severe TEAEs	0	0	0	0
All deaths (AEs leading to death)	0	0	0	0
Deaths (TEAEs leading to death)	0	0	0	0

AE=adverse event; BRV=brivaracetam; IMP=investigational medicinal product; PBO=placebo; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study participant reporting at least 1 TEAE in that category.
Note: All deaths were based on all study participants screened and refers to all deaths that occurred during the study.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: AEs that occurred during the Open-Label Temporary Period are not included.
Data source: Table 9.1.1.P

2.3.3. Discussion on clinical aspects

The MAH has submitted a report of the results of Study EP0083: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Parallel-Group Study to Evaluate the Efficacy and Safety of Adjunctive Brivaracetam in Subjects (≥16 to 80 Years of Age) with Partial Seizures with or without Secondary Generalization.

Twenty participants were between 16-18 years of age at the start of the study: 6 in the placebo group 14 in the BRV treatment groups. A total of 13 participants in the BRV treatment groups completed the study.

The safety profile of the 13 study participants <18 years of age who received BRV treatment and completed the EP0083 study was consistent with the established safety profile of BRV. No new safety concerns were identified in these participants.

The PK data were not summarized for participants <18 years of age due to the small size of the BRV treatment groups (9 and 4 participants in BRV 50mg/day and BRV 200mg/day groups, respectively). According to the MAH, the PK results for participants <18 years of age were consistent with those observed in BRV studies with participants >18 years of age.

The MAH is of the opinion that no change is deemed necessary to the Briviact Product Information in view of the data submitted. This is agreed. The descriptive results of the current study do not impact the current benefit-risk balance of BRV and no evidence of new safety concerns was found.

3. Rapporteur's overall conclusion and recommendation

The results of EP0083 are being submitted in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The results of the current study do not impact the current benefit-risk balance of BRV and no evidence of new safety concerns was found.

☒ **Fulfilled:**

No regulatory action required.