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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/P46/006

Note

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

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1. Introduction

In the EU, brivaracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy. In the US, Argentina, and Taiwan, it has also been approved as monotherapy for this indication and age group.

Brivaracetam (BRV) is a 2-pyrrolidone derivative, (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide), with a high and selective affinity for synaptic vesicle protein 2A (SV2A), a transmembrane glycoprotein found at presynaptic level in neurons and endocrine cells shown to modulate exocytosis of neurotransmitters. Binding to SV2A is hypothesized to be the primary mechanism for the anticonvulsant activity of BRV.

On 24 September, the MAH submitted an Article 46 paediatric dossier for study EP0088, which was completed on 17 Apr 2020, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of the completed post-authorisation observational study.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

According to the MAH, EP0088 was a post-marketing, prospective, multicenter non-interventional study conducted in the US, with a 12-month observation period for patients initiating treatment with brivaracetam (BRV), to collect information on real-world outcomes in patients with partial-onset seizures (POS) treated with BRV in clinical practice.

In the study EP0088, one single patient was under the age of 18 at the time of informed consent.

2.2. Information on the pharmaceutical formulation used in the study<ies>

The prescribed treatments were provided by the treating physician with commercially available products (BRV with the trademark Briviact).

2.3. Clinical aspects

2.3.1. Introduction

For the current submission, the MAH submitted a clinical overview, summarizing the disposition and TEAEs for the one participants in EP0088 who was <18 years old at the time of informed consent in order to fulfil the requirement of reporting paediatric data as outlined in Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The MAH also submitted a final report for study EP0088 providing data from the overall participant population.

2.3.2. Clinical study

EP0088: ***a postauthorization observational multicenter study of brivaracetam (BRV) and was designed to collect information on real-world outcomes in patients with partial-onset***

seizures (POS) who were treated with BRV in clinical practice after the product was marketed in the US.

Description

A postauthorization observational multicenter study to collect information on real-world outcomes in patients with partial-onset seizures who were treated with BRV as prescribed according to ordinary clinical practice in the US.

Methods

Objective

The primary objective was to evaluate BRV retention in daily clinical practice 12 months after the initiation of BRV.

The secondary objectives were to determine the association between BRV retention and 1) the time to discontinuation of levetiracetam (LEV), oxcarbazepine (OXC), carbamazepine (CBZ) and/or lamotrigine (LTG) [≤ 6 months, > 6 months after initiation], and 2) the reason for discontinuation for past use of LEV, OXC, CBZ, and/or LTG.

The other objectives were to characterize BRV retention in daily clinical practice, to evaluate seizure control on BRV treatment, to assess the effect of BRV on the patients' perception of their physical, mental, and social health, and patient-reported seizure-related disability, to summarize health resource use (e.g. unplanned hospitalizations, proportion of patients hospitalized, length of hospital stay, and number of emergency room visits due to epilepsy), and to determine whether patients enrolled and receiving LEV experienced AEs or seizure exacerbation during conversion from LEV to BRV.

Study design

EP0088 was a postmarketing, multicenter, prospective, observational and non-interventional study conducted in the US, with an estimated 18-month enrolment period and a 12-month observation period from the initiation of BRV. The normal clinical practice at the start of the study was to prescribe BRV as adjunctive therapy, but it was approved as monotherapy during the study. The clinical care of patients with epilepsy was performed by their treating physician following standard clinical practice, and up to 6 routine clinical visits (in-person, by telephone, or by video chat) was anticipated for the study. Patients were selected based on physician and patient decision to initiate therapy with BRV in the reviewed clinics. Consenting patients were evaluated before BRV initiation or within 2 days of BRV initiation. The evaluations were in-person, by telephone or video chat, on around 1.5, 3, 6 and 12 months since the initiation of BRV, depending on clinical practice. An unscheduled contact may have been performed following any adjustment to BRV or another AED.

All patients were followed for up to 12 months from BRV initiation regardless of changes in their treatment regimen. The treatment and follow-up were performed as per current clinical practice without any extra measures apart from requesting completion of questionnaires. The choice of medical treatment was not influenced by the study. There was one treatment group, and one interim analysis was conducted after 150 patients had initiated BRV to assess early treatment effectiveness.

Three amendments to the protocol were made. Firstly, the inclusion/exclusion criteria were changed and the follow-up time shortened to 12 months to enhance enrolment. Secondly, the data collection schedule was clarified as to be based on BRV initiation, and thirdly, the visit 1 was allowed to be conducted remotely. Minor edits and administrative changes were also made.

Study population /Sample size

Up to 350 consenting patients were to be enrolled.

Treatments

There were no assigned treatments because of the participation in this non-interventional study. The prescribed treatments were provided by the treating physician with commercially available products (BRV with the trademark Briviact).

Outcomes/endpoints

The primary variable was BRV retention 12 months after the initiation of BRV. The secondary variables were BRV retention at 3 and 6 months from initiation.

Other recorded parameters were demographics and baseline seizure characteristics, concomitant AEDs, reason for AED discontinuations, BRV starting dose and modal doses, Seizure-related Disability Assessment Scale (SERDAS) scores at 1.5, 3, 6, and 12 months and changes from baseline at each timepoint; Patient-Reported Outcomes Measurement Information System (PROMIS) T-scores at 1.5, 3, 6, and 12 months and change from baseline at each timepoint; absolute reduction in POS frequency from baseline to 3,6, and 12 months; response based on percent reduction in POS at 3, 6, and 12 months (response interpreted as ≥ 50% reduction); proportion of seizure-free patients at 3, 6, and 12 months after initiation of BRV; time to BRV discontinuation; the number of unplanned hospitalizations, proportion of patients hospitalized, number of emergency visits due to epilepsy up to 12 months after BRV initiation.

The safety variables were incidence of adverse events (AEs) or serious adverse events (SAEs), including adverse events of special interest (AESI); incidence of AEs leading to BRV discontinuation, and time to discontinuation of BRV due to AEs.

Other relevant safety information included the following: pregnancy or lactation exposure; medication errors, overdose, abuse, misuse, or occupational exposure; lack of therapeutic efficacy; suspicion of transmission of an infectious agent by the medicinal product, or a suspicion of an AE associated with a suspected or confirmed falsified medical product or one with a quality defect; off-label use or misuse, or unexpected therapeutic effect. AESIs were defined as autoimmune, allergic, tubulointerstitial, or any nephritis, tubulointerstitial nephritis and uveitis syndrome, and Hy's Law.

Statistical Methods

All variables were summarized using descriptive statistics. Statistical models were run for exploratory purposes. Generally, univariate analysis was conducted to assess the crude relationship between the predictors and the outcomes. Multivariable analysis was used to assess the relationship between predictors and outcome variables after controlling for potential confounders.

Results

Recruitment/ Number analysed

The total number of 304 consenting patients had a documented baseline visit, and 254 of them received at least one dose of BRV within the study. A total of 162 patients (63.8%) who received BRV completed the study, whereas 36.2% discontinued prematurely. Fifty-nine patients discontinued BRV documentedly (23.2%), and 36 six dropped out of the study (14.2%), most commonly because of side effects (10.6%).

Of the patients who received BRV in the study, 228 (89.8%) were younger the 65 years of age. Of this population, only one patient who was <18 years old fulfilled the criteria set for reporting paediatric data as outlined in Article 46 of Regulation (EC) No 1901/2006.

Baseline data

The paediatric patient in EP0088 was a, who had been at the time of epilepsy diagnosis (International League Against Epilepsy seizure classification IB); the etiology was genetic (familial epilepsy).

The patient's 28-day adjusted Baseline POS frequency was calculated as 0.15 seizures. The historical ictal and inter-ictal electroencephalogram results were abnormal, with POS impairing awareness, POS evolving to bilateral convulsive seizure and focal spikes; the patient's magnetic resonance imaging results were abnormal and clinically significant (focal). The patient had 4 concomitant AEDs at baseline (LCM, TPM, LEV, LTG).

Efficacy results

The patient achieved BRV retention at 12 months and was censored at the last date of administration (Day 365).

The seizure-related efficacy variables are shown in the Table below.

Visit [Relative day]	28-day adjusted POS frequency	Absolute reduction	Percent reduction	Seizure freedom	Response in POS [a]
Visit 1 (Baseline) [1]	0.15	-	-	-	-
Visit 3 (Month 1.5) [78]	0.00	0.15	100.00	Yes	Yes
Visit 4 (Month 3) [104]	3.23	-3.08	-2023.08	No	No
Visit 5 (Month 6) [219]	1.70	-1.55	-1020.00	No	No
Visit 6 (Month 12) [365]	0.00	0.15	100.00	Yes	Yes

POS=partial-onset seizure

[a] Response was defined as ≥50% reduction from Baseline in POS frequency.

The SERDAS scores evaluating disability related to seizures during the past month before the assessment, with changes from baseline visit, are shown in the table below.

Visit	SERDAS Question						SERDAS Total score (days)	Total score change from Baseline (days)
	1	2	3	4	5	6		
Visit 1 (Baseline)	13	0	13	0	0	5	26	-
Visit 3 (Month 1.5)	1	1	2	0	1	5	5	-21
Visit 4 (Month 3)	0	0	10	3	0	8	13	-13
Visit 5 (Month 6)	3	0	2	0	0	1	5	-21
Visit 6 (Month 12)	0	8	6	0	0	5	14	-12

SERDAS=Seizure-related Disability Assessment Scale
Note: SERDAS Total score (ie, number of days impacted) is the sum of Questions 1 through 5.

The PROMIS scores evaluating the patient's response to questions related to anxiety, anger, depression, fatigue, and sleep disturbance in the past 7 days, are shown in the table below.

Visit	Anxiety Short Form	Anger Short Form	Depression Short Form	Fatigue Short Form	Sleep Disturbance Short Form
Visit 1 (Baseline; observed result)	59.5	62.9	55.7	57	63.8
Visit 3 (Month 1.5)	0	-12.4	1.6	-3.9	5
Visit 4 (Month 3)	3.9	-16.6	-3.9	3.7	-2.1
Visit 5 (Month 6)	-3.7	-16.6	-14.7	12	2.2
Visit 6 (Month 12)	-3.7	-12.4	-3.9	-3.9	9.5

PROMIS=Patient-Reported Outcomes Measurement Information System

The overall score indicates mild to moderate symptoms or impairment at baseline. An overall worsening with a T-score of 73.3 was evident at visit 6. One hospitalization was reported before BRV treatment but not during the rest of the study.

Safety results

The dose of BRV was 50 mg/day, and the total exposure was 365 days in this patient case without any adverse events, events related to any safety aspect, or of special interest, being reported during the study.

CHMP comment:

The single adolescent patient had experienced seizures before two of the visits after baseline whereas none before two of the visits after baseline. The overall seizure-related disability was reduced, as reflected by the SERDAS score, and the disability profile changed into weighting the medication-related effects. The PROMIS short form score showed an improvement in the Anger form, and an overall worsening in Sleep Disturbance form. No treatment-emergent adverse event were reported in this case. Obviously, no concerns are raised on the risk profile of BRV nor can conclusions be drawn on efficacy. The potential adverse events implied by changes in scoring are reflected in the present SmPC.

2.3.3. Discussion on clinical aspects

One patient who was <18 years old was included in the non-interventional study EP0088 (with the analyzed total safety population of 254).

The efficacy results are reasonably in line with the main study. As for the safety, no AEs were reported in this case. The changes of profile in the PROMIS scoring during follow-up are as expected.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of EP0088 in order to fulfil the requirement of reporting paediatric data as outlined in accordance with Article 46 of regulation (EC) no 1901/2006, as amended. The number of paediatric subjects <18 years of age was limited to a single patient; the case which did not have reported TEAEs does not give rise to new concerns.

The MAH does not propose any changes of the currently approved SmPC based on the present data, which is supported.

☒ **Fulfilled:**

No regulatory action required.