Amsterdam, 21 August 2025
EMADOC-1700519818-2194634
Human Medicines Division

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

Briviact

Brivaracetam

Procedure no: EMA/PAM/0000278054

Note

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

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1. Introduction

On 30 May 2025, the MAH submitted a completed paediatric study (EP0085) for Briviact, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that An Open-Label, Multicenter, Follow-Up Study to Evaluate the Long-Term Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Subjects ≥16 Years of Age with Partial Seizures with or without Secondary Generalization (EP0085) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Brivaracetam ((2S) 2 [(4R) 2 oxo 4 propyltetrahydro 1H pyrrol 1 yl] butanamide) is a 2 pyrrolidone derivative and displays a high and selective affinity for the SV2A in the brain. Binding to SV2A is believed to be the primary mechanism for brivaracetam anticonvulsant activity.

Oral film-coated tablets of brivaracetam 25mg and brivaracetam 50mg were used in this study.

The targeted therapeutic indications for brivaracetam are monotherapy and adjunctive therapy in the treatment of focal/POS with or without secondary generalization in patients from 1 month of age with epilepsy.

CHMP comment

Standard film-coated tablets of brivaracetam 25mg and 50mg strength were used in the study. No specific formulations for children were used.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- An Open-Label, Multicenter, Follow-Up Study to Evaluate the Long-Term Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Subjects ≥16 Years of Age with Partial Seizures with or without Secondary Generalization (EP0085)

2.3.2. Clinical study

EP0085 - An Open-Label, Multicenter, Follow-Up Study to Evaluate the Long-Term Safety and Efficacy of Brivaracetam Used as Adjunctive treatment in Subjects ≥16 Years of Age with Partial Seizures with or without Secondary Generalization

Description

EP0085 was an open label, multicentre, follow up study to evaluate the long-term safety and efficacy of brivaracetam used as adjunctive treatment in participants ≥16 years of age with partial seizures with or without secondary generalization. EP0085 included both paediatric participants (≥16 years of age), and adult participants.

The following study periods were defined:

- SV (Visit 0, up to 3 weeks before the EV for direct enrollers in Japan only).
- Evaluation Period (Visit 1 to End of Study Visit or EDV): Participants who entered EP0085 from EP0083 and N01379 entered directly into the Evaluation Period.
- Down-Titration Period (up to 4 weeks):
  - If a participant discontinued brivaracetam, the Investigator planned an EDV followed by a progressive down-titration of brivaracetam.
  - During the Down-Titration Period, the brivaracetam dose may have been decreased in steps of a maximum of 50mg/day on a weekly basis. A last down-titration step at 25mg/day for 1 week should have been included prior to the 2-week Study Drug-Free Period.
- 2-week Study Drug-Free Period: After completion of the Down-Titration Period, or for those participants who for extenuating circumstances did not complete a Down-Titration Period, the participant was required to enter a 2-week Study Drug-Free Period, followed by the FV.

Visits should have occurred on the specified Visit/Week. A ±7-day window for each specified Visit/Week was allowed, provided the participant had brivaracetam to sustain the visit window. The end of the study was defined as the date of the last visit of the last participant in the study.

Methods

Study participants

The study population included directly enrolled Japanese participants meeting the inclusion and exclusion criteria specified in EP0085 Final CSR Section 3.3.1, Japanese and Chinese rollover participants from EP0083 (provided they completed the Treatment and Transition Period of EP0083 prior to enrollment in EP0085), and Japanese rollover participants from N01379.

Because the primary objective of EP0085 was to evaluate the long-term safety and tolerability of brivaracetam, rather than brivaracetam efficacy, a lower Baseline POS frequency was defined in the inclusion criteria for EP0085 direct enrollers compared with the Baseline POS frequency defined in the inclusion criteria of the core studies for the rollover groups. This was also done to avoid having overlapping eligibility requirements between EP0085 and EP0083, the latter of which was still enrolling study participants in parallel with EP0085. Therefore, the direct enrollers group was considered to be uninformative for the evaluation of brivaracetam efficacy because of low Baseline seizure frequency. However, the safety and efficacy data for all study groups are provided side by side in the EP0085 Final CSR for purposes of comparison and transparency.

CHMP comments

The paediatric population included only adolescents from 16 years old. 6 out of 7 patients were Japanese and one – Chinese.

Treatments

Oral film-coated tablets of brivaracetam 25mg and brivaracetam 50mg were used in this study.

Directly enrolled participants in Japan and rollover participants from EP0083 were started on brivaracetam 100mg/day (50mg bid) at Visit 1 (study entry) and were maintained at this dose for at least 2 weeks unless the participant was unable to tolerate treatment.

Japanese rollover participants from N01379 were started at a dose up to brivaracetam 200mg/day at Visit 1; the next visit for these participants was Visit 4 (Visit 2 and Visit 3 were not conducted). The brivaracetam dose could have been adjusted between 50mg/day and 200mg/day based on the individual participant's seizure control and tolerability; however, dose decreases should not have exceeded 50mg/day. Brivaracetam must always have been administered in equal morning and evening doses except in the last week of down titration when brivaracetam was given only in the morning.

Study participants who were converted to the commercial brivaracetam product completed an End of Study Visit without entering the Down-Titration Period or the 2-week Study Drug Free Period and did not complete a Final Visit.

Objective(s)

The primary objective was to evaluate the long-term safety and tolerability of brivaracetam in focal epilepsy participants with POS.

The secondary objective was to evaluate the maintenance of efficacy of brivaracetam over time.

Outcomes/endpoints

The primary safety variable was TEAEs.

The other safety variables were as follows:

- Laboratory tests (blood chemistry, hematology, and urinalysis)
- Vital signs
- Body weight
- 12 lead ECG
- Physical examination
- Neurological examination

The efficacy variables for rollover participants in Japan and China included:

- Percent reduction in POS frequency per 28 days from Baseline of EP0083 or N01358 to the Evaluation Period.
- Responder rate in POS frequency per 28 days over the Evaluation Period. A responder was defined as a participant with a ≥50% reduction in POS frequency from the Baseline Period of EP0083 or N01358.

Efficacy variables for direct enrollers in Japan included:

- Percent reduction in POS frequency per 28 days from 8 weeks prior to brivaracetam administration to the Evaluation Period.
- Responder rate in POS frequency per 28 days over the Evaluation Period. A responder was defined as a participant with a ≥50% reduction in POS frequency from 8 weeks prior to brivaracetam administration.

Efficacy variables for all participants (rollovers in Japan and China and direct enrollers in Japan) included:

- Percentage of participants continuously seizure free for POS and all seizure types (partial, generalized, and unclassified epileptic seizure) for ≥6 months and ≥12 months during the Evaluation Period.
- Seizure freedom (partial, all epileptic seizure) during the Evaluation Period.

CHMP comment

The study objectives primarily focused on long-term safety of treatment and are acceptable. The secondary objectives included evaluation of maintenance of efficacy too.

Sample size

For this open-label LTFU study, no sample size calculation was performed. The sample size depended on recruitment into and completion of the previous studies. Overall, approximately 217 participants were planned for enrollment. In Japan, it was estimated that approximately 127 participants would enter the study. This estimate assumed that at least 90% of randomized Japanese participants would complete EP0083 (approximately 90 participants) or enroll from N01379 sites in Japan (7 participants) and that 30 Japanese participants would be directly enrolled in this study. Likewise, this estimate assumed that at least 90% of randomized Chinese participants would complete EP0083 (approximately 90 participants).

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

Descriptive statistics were displayed to provide an overview of the study results. All summaries were descriptive; no statistical hypothesis testing was planned.

Results

Participant flow

Recruitment

Seven paediatric participants (<18 years of age) were enrolled in EP0085. Due to the small number of paediatric participants in the study, no data are summarized; data are provided by participant and identified in the Clinical Overview Addendum by a letter from "A" to "G".

Baseline data

Of these 7 paediatric participants enrolled in EP0085, 6 participants were rollovers from EP0083 and 1 participant was a direct enroller. Five participants completed the study, 1 participant discontinued due to an AE, and 1 participant discontinued with a reason of withdrawal by participant.

All paediatric participants were 16 to <18 years of age at the time of enrollment in EP0085; 5 were female and 2 were male (Table 4 2). The majority of paediatric participants were Japanese.

Baseline POS frequency differed between the direct enrollers and the rollover groups. Therefore, the direct enrollers group (N=1 paediatric participant) was considered to be uninformative for the evaluation of brivaracetam efficacy because of low Baseline seizure frequency.

All efficacy analyses of the Evaluation Period were based on the seizure records during the Evaluation Period on/after the first dose of brivaracetam in EP0085.

For rollovers, the Baseline Period was obtained from the core studies of EP0083 and N01358. For direct enrollers, the Baseline Period was defined as seizure counts collected from 8 weeks prior to the first brivaracetam administration in EP0085.

CHMP comments

Only 7 paediatric patients were included into the study. All baseline data are presented for each individual patient. Six out of 7 patients were 17 years old with epilepsy duration ranging from 0.4 to 16.5 years. There were 6 Japanese and one Chinese patients. All patients had been treated with other concomitant antiseizure medications (one - n=2, two – n=3 and three n=2).

Number analysed

Only 7 paediatric patients were recruited.

Efficacy results

All efficacy analyses of the Evaluation Period were based on the seizure records during the Evaluation Period on/after the first dose of brivaracetam in EP0085.

For rollovers, the Baseline Period was obtained from the core studies of EP0083 and N01358. For direct enrollers, the Baseline Period was defined as seizure counts collected from 8 weeks prior to the first brivaracetam administration in EP0085.

A by-participant listing of individual efficacy outcomes for paediatric participants at Baseline and during the Evaluation Period is presented in Table 4 5. Of the 6 paediatric participants enrolled in EP0085 who were rollovers from EP0083, 5 participants had a reduction in the 28-day adjusted POS frequency and 4 participants were ≥50% reduction responders (Table 4-5).

During the Evaluation Period, one participant (EP0083 PBO group) was continuously POS-free and all-type seizure free for ≥12 months, and another participant (EP0083 brivaracetam 200mg/day group) was continuously POS-free and all-type seizure free for ≥30 months. No other paediatric participants were continuously POS-free or all-type seizure free for ≥6 months (the lowest time interval).

CHMP comments

Since one of the secondary efficacy objectives was to evaluate proportion of patients continuously seizure free for POS and all seizure types (partial, generalized, and unclassified epileptic seizure) for ≥6 months and ≥12 months during the Evaluation Period, it is noted that only 2 patients were seizure free – one for ≥12 months and another for ≥30 months.

These observations in individual patients do not allow to make any conclusions on the maintenance of treatment effect in paediatric patients.

Safety results

Seven paediatric participants (<18 years of age) were enrolled in EP0085. Due to the small number of paediatric participants in the study, no data are summarized; data are only provided by participant and identified in the Clinical Overview Addendum by a letter from "A" to "G".

The duration of brivaracetam exposure for each paediatric participant during EP0085 is presented below:

CHMP comment

The exposure of patients varied from 29 to 1878 days. 6 out of 7 patients were treated for more than 9 months. Thus, it is possible to state that at least 6 paediatric patients contributed with information regarding long-term safety of treatment. It is noted that one patient who was treated only for 29 days discontinued treatment due to adverse effects.

Among the 7 paediatric participants, the TEAEs, by PT, reported by ≥2 paediatric participants were corona virus infection (4 participants) and headache (2 participants; 1 participant reported 2 events), dizziness (2 participants), and pyrexia (2 participants; 1 participant reported 2 events) (Table 5 1). Considering that the study occurred during the COVID 19 pandemic, it was not unexpected that corona virus infection was the most frequently reported TEAE. Differences in regional public health policies implemented may have impacted local incidences of reported corona virus infections.

The majority of TEAEs were nonserious, considered not related to brivaracetam by the Investigator, did not lead to discontinuation, and had outcomes of recovered/resolved. All TEAEs were reported with a maximum intensity of mild or moderate. Participant C had nonserious TEAEs of malaise and headache that were considered related to brivaracetam; the TEAE of malaise led to brivaracetam being withdrawn and the participant discontinuing the study.

One participant had 1 TEAE of seizure that was serious, was considered not related to brivaracetam, and did not lead to discontinuation.

CHMP comments

All seven patients reported AEs which were mild to moderate severity. Only one case of serious seizure event was reported. It is acknowledged that the study was performed during COVID -19 pandemic and some reported AEs are related to corona virus infection. The patient who discontinued treatment after 29 days had headache and malaise AEs reported according to Table 5-1 and discontinued treatment due to malaise.

No deaths were reported for participants during EP0085.

No positive pregnancy tests were reported during EP0085.

No paediatric participants had PCST hematology values.

Two paediatric participants had PCST biochemistry values; none were associated with a TEAE:

No other paediatric participants had a PCST biochemistry value.

No paediatric participants had TEAEs associated with urinalysis values.

No paediatric participants had events meeting the criteria for PDILI.

Three paediatric participants had PCST body weight values; none were associated with a TEAE (EP0085 Final CSR Table 8.1.3, EP0085 Final CSR Listing 6.4, and Table 5 1):

No other paediatric participants had a PCST body weight value, and no paediatric participants had a PCST vital signs value.

No paediatric participants had clinically significant ECG findings. Two paediatric participants had abnormal but not clinically significant ECG findings.

No paediatric participants had clinically significant abnormal physical or neurological examination findings during the Evaluation Period.

No paediatric participants had abnormal C-SSRS findings that would suggest suicidality and no paediatric participants reported TEAEs of self-injurious ideation, suicidal ideation, or suicide attempt.

2.3.3. Discussion on clinical aspects

EP0085 was an open-label, multicentre, follow-up study to evaluate the long-term safety and efficacy of brivaracetam used as adjunctive treatment in subjects ≥16 years of age with partial seizures with or without secondary generalization.

The goal of the EP0085 was to provide evidence of the long-term safety and efficacy of brivaracetam as adjunctive therapy in Japanese and Chinese patients with POS. Since EP0085 included paediatric participants (≥16 to <18 years of age), the Applicant submitted the results of study in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation).

The study objectives primarily focused on long-term safety of treatment. The efficacy variables were described as secondary.

Seven paediatric patients were enrolled into this study. The information on efficacy was provided for each individual patient. No meaningful summaries are possible to make from these numbers. 5 out of 7 participants had a reduction in the 28-day adjusted POS frequency and 4 participants were ≥50% reduction responders, all of whom were in the EP0083 rollovers group. The small number of patients does not allow to make any conclusions regarding the observed efficacy. It can be only concluded that no new information regarding the efficacy is reported.

6 out of 7 patients were treated for more than 9 months (more than 283 days), thus, contributing with information regarding long-term safety of treatment. The safety profile observed in the 7 paediatric participants enrolled in EP0085 was generally consistent with the safety profile of brivaracetam in adult and paediatric patients described in the SmPC. All seven patients reported AEs which were mild to moderate severity. It is acknowledged that the study was performed during COVID-19 pandemic and some reported AEs are related to corona virus infection.

Among serious TEAE one patient reported seizures event. No deaths were reported in the study.

In summary, small number of patients preclude from any meaningful conclusions. No new information regarding efficacy of brivaracetam were reported and the safety findings in EP0085 were generally consistent with the known safety profile of brivarecetam.

3. Rapporteur's overall conclusion and recommendation

No new efficacy or safety concerns were identified in the study EP0085. Safety profile of the paediatric patients who received BRV treatment and completed the EP0085 study was in line with the established safety profile of BRV. Therefore, the benefit-risk ratio remains unchanged. No changes in the SmPC is considered necessary.

☒ **Fulfilled: No regulatory action required.**