30 January 2020
EMA/691193/2019
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/P46/005

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 (BRV) 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.

Brivaracetam 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 19 November 2019, the MAH submitted an Article 46 paediatric dossier for study N01125, which was completed on 28 May 2019, 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

According to the MAH, N01125 was a Phase 3, open-label, multicenter, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of BRV used as adjunctive treatment at a flexible dose up to a maximum of 200mg/day in study participants aged 16 years or older diagnosed with epilepsy or Unverricht-Lundborg disease (ULD). An abbreviated clinical study report (CSR) based on a clinical cutoff date of 17 Jan 2014 was previously submitted for N01125 for the purpose of providing supportive information for the BRV partial-onset seizures (POS) adjunctive therapy Marketing Authorization Application (MAA) submission. The MAH has now provided the final CSR based on the completed study.

In the study N01125, a total of 7 patients were under the age of 18 at the time of informed consent.

2.2. Information on the pharmaceutical formulation used in the study

Oral film-coated tablets of BRV 2,5 mg, 10mg, 25mg, and 50mg were used. The batch numbers are provided in a table 3.3 of the CSR.

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 7 participants from N01125 who were <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 N01125 providing data from the overall participant population.

2.3.2. Clinical study

N01125: ***a Phase 3, open-label, multicenter, long-term follow-up (LTFU) study to evaluate the long-term safety and efficacy of brivaracetam (BRV) used as adjunctive treatment at a flexible dose up to a maximum of 200mg/day in study participants aged 16 years or older diagnosed with epilepsy or Unverricht- Lundborg disease (ULD).***

Description

A Phase 3, open-label, multicenter, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of BRV used as adjunctive treatment at a flexible dose up to a maximum of 200mg/day in study participants aged 16 years or older diagnosed with epilepsy or Unverricht- Lundborg disease (ULD).

Methods

Objectives

The primary objective was to evaluate the long-term safety and tolerability of BRV at individualized doses with a maximum of 200mg/day in participants suffering from epilepsy.

The secondary objective was to evaluate the maintenance of efficacy over time of BRV (for POS/primary generalized seizure [PGS] participants). However, no efficacy objectives were defined for participating patients with ULD.

The exploratory objectives were to explore the impact on health-related quality of life, as well as to collect data on medical resources used and on indirect costs.

Study design

N01125 was an open-label, single-arm, multinational, multicenter, non-comparative, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of BRV used as adjunctive treatment at a flexible dose up to a maximum of 200mg/day in study participants aged 16 years or older diagnosed with epilepsy or Unverricht-Lundborg disease (ULD). The study population of N01125 consisted of participants 16 years of age and older with epilepsy from the previous studies N01114, N01187, N01236, N01252, N01315 and N01254, mainly with POS, a minority with generalized epilepsy (from N01254), and ULD (from N01187, N01236).

Assessor's comment

There were 6 feeding studies for N01125 with a total of 1250 patients with partial-onset and or generalized epilepsy or Unverricht-Lundborg disease. Overall, all of these studies had a very minor quota of participants under 18 years of age. Of the seven patients under scrutiny in this submission, 5 had partial-onset epilepsy (POS) and 2 Unverricht-Lundborg disease (ULD).

The following study periods were defined:

- Evaluation Period (visit 1 until the last evaluation period visit or early discontinuation visit), considered in 3-month periods. The visit 1 was performed on the same day as the last visit of the previous study in which the participant was enrolled
- Down-titration period: if the study participant was discontinuing study drug, the Investigator planned an early discontinuation visit and the progressive down-titration of study drug, during which the drug dose may have been decreased in steps of a maximum of 50mg/day on a weekly basis

- Post-treatment period (2 to 4 weeks): after completion of the down-titration period, the study participant entered a post-treatment period for a minimum of 2 weeks and a maximum of 4 weeks, followed by a final visit

The individual starting dose for each participant was the dose recommended at the end of their previous study. The recommended maximum dose of BRV at the outset was 400mg/day; however, all participants had doses less than 200 mg/day at the stage when the protocol was amended to allow for a maximum dose of BRV 150mg/day (Protocol Amendment 1, 01 Apr 2005) and subsequently for that of BRV 200mg/day (Protocol Amendment 25, 03 Jan 2011) in participants with epilepsy. Daily administration in 2 equal intakes was recommended. Dose adjustment of study drug and/or concomitant antiepileptic drugs (AEDs) or antimyoclonic drugs was allowed at any time to improve seizure control if needed or in case of a safety or tolerability issue.

Discontinuation of treatment with BRV was marked by a Down-Titration Period: the dose of BRV was decreased in steps of a maximum of 50mg/day on a weekly basis with a last down titration step at 20mg/day for 1 week. Participants who completed the Down-Titration Period entered a Post-Treatment Period for a minimum of 2 weeks and a maximum of 4 weeks and subsequently, the final visit occurred. Dose adjustment to concomitant AEDs may have been made at any time during the study and participants may have started new AEDs. Concomitant AEDs may have also been discontinued however, special considerations applied if the discontinuation of such AEDs resulted in the participant receiving BRV monotherapy. Before Substantial Protocol Amendment 24, in the event of excellent efficacy and tolerability of BRV, withdrawal of concomitant AEDs resulting in monotherapy of BRV may have been attempted by the Investigator. With Substantial Protocol Amendment 24, conversion to monotherapy was no longer permitted; however, participants already on BRV monotherapy were allowed to continue on monotherapy. For each study participant, the study ran throughout the duration of the clinical development period of BRV, and continued until a marketing authorization was granted by any Health Authority in an indication for the adjunctive treatment in adults with refractory POS, whether or not secondarily generalized, until the Sponsor decided to close the study, until a managed access program, named patient program, compassionate use program, or similar type of access program was established as allowed per country-specific requirement in addition to legal and regulatory guidelines, or until BRV development was stopped by the Sponsor. The study duration for each participant was variable; the maximum study duration was 14 years.

Study population /Sample size

The study N01125 enrolled male or female study participants with partial onset epileptic seizures, aged 16 years or older, who had completed the Treatment Period in brivaracetam trials allowing access to this study (N=853). The Investigator could enrol subjects whom he/she expected to reasonably benefit from the long-term administration of BRV. Study participants with severe medical, neurological, and psychiatric disorders, including current suicidal ideation or behaviour, or laboratory values which may have had an impact on the safety of the study participant, as determined by the Investigator, were excluded, as well as subjects who had shown poor compliance in the previous trial or were participating in any clinical trial of another investigational drug or device concomitantly, and females of childbearing potential without a medically accepted contraceptive method in use.

Treatments

Study participants were continued on the individual BRV starting doses which was for each patient the dose that was recommended at the end of their previous study. They were maintained at this dose for at least 2 weeks, unless the study participant was not able to tolerate treatment. The BRV dose could subsequently have been adjusted based on the individual study participant's seizure control and/or

tolerability. The recommended maximum dose of BRV at the outset was 400mg/day; however, all participants had doses less than 200 mg/day at the stage when the protocol was amended to allow for a maximum dose of BRV 150mg/day (Protocol Amendment 1, 01 Apr 2005) and subsequently for that of BRV 200mg/day (Protocol Amendment 25, 03 Jan 2011) in participants with epilepsy. Daily administration in 2 equal intakes was recommended. Dose adjustment of study drug and/or concomitant antiepileptic drugs (AEDs) or antimyoclonic drugs was allowed at any time to improve seizure control if needed or in case of a safety or tolerability issue.

Outcomes/endpoints

The safety variables of N01125 were the following:

- occurrence of adverse events
- laboratory tests (blood, urinalysis)
- vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) and body weight
- electrocardiogram (ECG)
- physical and neurological examinations
- plasma concentration of brivaracetam and concomitant AEDs

The primary efficacy variable was based on the seizure frequency per week for partial onset seizures (type I) by 3-month periods over the Evaluation Period.

The secondary efficacy variables were the following:

- seizure frequency (all three types) per 3-month periods during the Evaluation Period
- proportion of seizure-free days (all three types) per 3-month periods during the Evaluation Period
- continuously seizure-free subjects for all seizures (all three types) by 3-month period over the Evaluation Period.
- responder rate for POS (Type I) frequency over the Evaluation Period. A responder was defined as a participant with a ≥50% reduction in seizure frequency from the Baseline Period of the previous study

The exploratory variables were the following:

- Health-Related Quality of Life (QOLIE-31-P) at month 3, at every yearly evaluation visit or at early discontinuation visit
- medical resources used by 3-month period over the Evaluation Period, including health care provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications and hospitalizations
- indirect costs by 3-month period over the Evaluation Period, including workdays or schooldays lost and days lost due to inability to perform a usual activity (excluding paid work)

Statistical Methods

All efficacy, safety and demographic variables were summarized by descriptive statistics.

Seizure frequency for all seizures was derived as the number of seizures standardized to a seven-day period, calculated as the number of seizures over the period, divided by the number of days in that period and multiplied by 7.

Percent reduction from Baseline for POS frequency was summarized by quantitative descriptive statistics for the categories of overall duration of exposure and by 3-month time intervals over the Evaluation Period. Similar summaries were provided for the full cohort interval and by 3-month time intervals for each exposure duration cohort and previous study cohort.

Responders over the Evaluation Period were defined as study subjects with ≥50% reduction in seizure frequency per week from baseline. A similar calculation was applied to each 3-month time interval over the Evaluation Period and for the cohort interval for each exposure duration cohort. Responder rate was summarized by 3-month periods. The maintenance of the efficacy over time was evaluated by means of the primary and secondary efficacy analyses.

The safety was analysed by summarizing by categories of total duration of exposure, including study-emergent adverse events. Abnormalities in clinical examinations and ECG were listed by period and visit. Separate tables were produced for adverse events leading to withdrawal and for those classified as serious (SAE), all categorized by duration of exposure.

Results

Recruitment/ Number analysed

The total number of recruited patients to the study N01125 was 853 participants, of which 729 were included in the POS efficacy analysis set, 30 in the primary generalized seizure (PG) category analysis set, and 94 to ULD efficacy analysis set.

Of the 7 study participants who were <18 years of age at the time of informed consent in N01125, 5 were POS patients and 2 were ULD patients. The 7 patients formed the paediatric safety analysis set. A summary of patient disposition and study completion is given in the table below. Out of the 7, 3 subjects completed whereas 4 subjects discontinued the study, 2 of these because of lack of efficacy.

Table 1: Summary of patient disposition and reasons for discontinuation (<18 years of age) (Safety Analysis Set)

	BRV N=7 n (%)
Completed study [a]	3 (42.9)
Discontinued study	4 (57.1)
Reason for discontinuation	
Adverse event	1 (14.3)
Lack of efficacy	2 (28.6)
Lost to follow-up	0
Participant choice	1 (14.3)
Other	0

BRV=brivaracetam
Note: Percentages were based on the number of participants in the Safety Analysis Set.
[a] A participant was a completer of the study if this participant completed the full extent of the study as defined in the protocol. Participants who transitioned to another BRV study or managed access program or similar type of program, or who converted to commercial BRV or entered a safety extension study, were considered study completers.

Data source: Table 1.2.P

Baseline data

The mean age for the participants in this safety analysis set was 16.6 years (range 16 -17 years). There were 5 male (71.4%) and 2 female (28.6%) subjects. Five subjects were white (71.6%), two of Asian race (28.6%). Overall, mean weight and height were 61.4 kg and 162.4 cm. Body mass index (BMI) category was in the range 18.5-25 kg/m^2 for 4 subjects (57.1%), between 25-30 kg/m^2 for 2 participants (28.6%), and between 30-40 kg/m^2 for 1 subject (14.3%); no participants were in the BMI categories of <18.5 kg/m^2 or ≥40 kg/m^2.

The mean duration of epilepsy for participants <18 years of age in the POS efficacy analysis set was 6.1 years (range 2-13 years), and the mean age at time of first seizure was 10.9 years (range 5-15 years). All subjects <18 years of age in the POS efficacy analysis set reported partial seizures at any time prior to entry into the preceding double-blind studies, including simple partial seizures (2 participants [40.0%]), complex partial seizures (4 participants [80.0%]), and partial evolving to secondary generalized seizures (5 participants [100.0%]). One subject (20.0%) <18 years of age reported generalized seizures prior to entry into the preceding double-blind studies.

At the baseline of the previous study, in the POS patients >18 years of age, the classification of the epileptic syndrome POS Efficacy Analysis Set, the classification of epileptic syndrome was unknown for 1 subject (20.0%) whereas 4 subjects had localization-related epileptic syndromes, the majority of which were symptomatic (3 participants [60.0%]) and one cryptogenic (1 participant [20.0%]). In this set, 2 participants (40.0%) had known seizure focus localization, in both cases temporally located, at the baseline of the previous double-blind study. The aetiology of epilepsy was unknown in two participants (40.0%) in the POS Efficacy Analysis Set, and the known aetiologies were congenital malformation, perinatal asphyxia and cerebral infection (1 subject with each one aetiology [20.0%]).

Of the study participants <18 years of age with POS, 1 patient (20.0%) had taken either 0 to 1 AED, 3 patients had taken 2 to 4 AEDs (60.0%), and 1 patient (20.0%) had taken ≥5 AEDs. At entry into the preceding double-blind study, all 5 patients were taking at least 1 AED, including lamotrigine and sodium valproate/valproic acid (3 subjects [60.0%] each), followed by levetiracetam, and oxcarbazepine (2 subjects [40.0%] each) and topiramate (1 subject [20.0%]).

Efficacy results

At the individualized doses up to a maximum of 200mg/day in participants <18 years of age with POS, administration of BRV resulted in the following results in the 5 subjects of the POS Efficacy Analysis Set:

- during the Evaluation Period, participants reported a median (Q1, Q3) POS frequency of 6.3 (2.0, 12.6) seizures per 28-day period, ranging from 0 to 540 seizures, compared with baseline median (Q1, Q3) POS frequency of 12.6 (9.5, 50.1) seizures per 28-day period, ranging from 4 to 510 seizures

- during the Evaluation Period, participants reported a median (Q1, Q3) reduction in POS frequency from Baseline of 33.6% (-0.4%, 91.1%) per 28-day period. The mean (SD) reduction in POS frequency during the Evaluation Period was 42.9% (48.7%) per 28-day period
- the 50% responder rate for POS frequency during the Evaluation Period for participants with POS was 40.0% (2/5 participants). Two participants maintained their 50% responder status through 99 months with 1 study participant maintaining their responder status through 135 months
- seizure-freedom for any continuous 6-month period of treatment was reported for two subjects, one being seizure free for up to 60 months

Assessor's comment

No efficacy objectives were understandably defined for ULD. Consequently, the paediatric population in the long-term follow-up does not allow us to make statistical conclusions but serves as a series for a directional assessment of safety and tolerability.

Safety results

All subjects in the <18 years of age Safety Analysis Set (7 participants [100%]) received at least 1 dose of BRV. Total participant-years of exposure was 32.6 years.

The most common modal doses of BRV were 150mg/day (3 participants [42.9%]) and 100mg/day (2 participants [28.6%]). One subject (14.3%) each received a modal dose of 50mg/day and 200mg/day. No subjects received a modal dose of BRV ≤20mg/day or >200mg/day.

Most of the participants (5 participants [71.4%]) had at least 6 months of exposure to BRV, 3 participants (42.9%) had at least 96 months of exposure to BRV, and 1 participant (14.3%) completed at least 138 months of treatment.

Summary of TEAEs

A summary of the incidence of TEAEs in participants <18 years of age is presented in the table below.

	BRV N=7 n (%) [#]
Any TEAE	7 (100) [63]
Permanent discontinuation of study drug due to TEAEs	1 (14.3) [1]
Drug-related TEAEs[a]	4 (57.1) [15]
Severe TEAEs	4 (57.1) [4]
Treatment-emergent SAEs	3 (42.9) [3]
Drug-related treatment-emergent SAEs[a]	0
Deaths	0

BRV=brivaracetam; SAE=serious adverse event; TEAE=treatment-emergent adverse event
Note: n=number of participants reporting a TEAE for the specified category; #=number of individual TEAEs
[a] The relationship was assessed by the Investigator.
Data sources: Table 12.1.P

All 7 participants <18 years of age reported at least 1 TEAE (100.0% [63 events]), roughly consistently with the overall population (n=720 [84.4%]). Of the 63 events reported, 29 were reported in subjects with POS and 34 in subjects with ULD. Their incidence was highest during the first 3-month safety interval. Approximately half of participants reported TEAEs with a maximum intensity of severe (4 subjects [57.1%]; 3 events in participants with POS and 1 event in a participant with ULD), one TEAEs of moderate and two of mild intensity (in the overall population the number of TEAEs of severe intensity was 216 [25.3%]). In the paediatric group, all severe TEAEs resolved without sequelae. One subject in this group (14.3%) experienced a TEAE leading to permanent discontinuation of the drug (aggression, that was deemed drug-related by the Investigator, in a subject with ULD).

A total of 4 participants reported a TEAE that was considered by the Investigator to be drug-related (57.1% [15 events]; 5 events in 3 participants with POS and 10 events in 1 participant with ULD), including psychomotor irritability, weight decrease, myoclonus, aggression, and depression (1 subject [14.3%] each). None of the SAEs were considered drug-related by the Investigator (femur fracture, convulsion, depression). In the overall population, the number of treatment-emergent SAEs was 248 (29.1%).

A summary of TEAEs occurring in ≥2 of participants <18 years of age is given in the table below.

MedDRA (Version 15.0) Primary SOC PT	BRV N=7 n (%)
At least 1 event	**7 (100)**
Gastrointestinal disorders	**4 (57.1)**
Abdominal pain	2 (28.6)
Vomiting	2 (28.6)
Nervous system disorders	**4 (57.1)**
Myoclonus	2 (28.6)
Psychiatric disorders	**5 (71.4)**
Aggression	2 (28.6)
Depression	2 (28.6)

BRV=brivaracetam; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Note: n=number of participants reporting a TEAE in any study period.
Data sources: Table 12.2.P

TEAEs of Interest

Overall in participants <18 years of age, 2 subjects (28.6%) reported 2 TEAEs potentially associated with seizure worsening, convulsion in a subject (14.3%) with POS and grand mal convulsion in a subject (14.3%) with ULD. The TEAE of convulsion was deemed serious but neither of them were deemed drug-related or SAEs nor led to permanent discontinuation of the study drug.

Two participants (28.6%) reported TEAEs potentially associated with behavioural disorders (single events of aggression and agitation in one subject and 6 events of aggression in another; both with ULD). As evaluated per safety time interval, the TEAEs of aggression were reported between months 1 to 3, 7 to 9, 10 to 12, and 31 to 33 of exposure to BRV; the TEAE of agitation was reported between 31 to 33 months of exposure. These TEAEs were mild or moderate in intensity and not serious, but one of the 6 TEAEs of aggression in one subject, deemed drug-related by the Investigator, led to permanent discontinuation of the study drug.

One participant with POS (14.3%) reported a single TEAE potentially associated with cognitive impairment (amnesia) occurring after an unknown number of days after the first dose of BRV. It was mild in intensity, not considered serious or related to the study drug by the Investigator.

Three participants (42.9%; two with POS, one with ULD) reported TEAEs potentially associated with suicidality or suicidal ideation, including depression (2 participants [28.6%], in one reported as severe, in the other as an SAE), overdose of valproate and suicidal ideation (1 subject [14.3%] each). None of these TEAEs led to permanent discontinuation of the study drug.

No participants <18 years of age reported TEAEs potentially associated with hepatotoxicity or renal injury. Pregnancies were not reported.

Three participants reported 7 TEAEs potentially associated with abuse potential: aggression and depression (two subjects [28.6%] each), as well as asthenia, somnolence, overdose, amnesia, and agitation (1 subject [14.3%] each). Events of aggression and depression were considered drug-related by the Investigator. One reported depression was severe but not considered drug-related, and all other TEAEs potentially associated with abuse potential were mild or moderate. One reported TEAE, aggression, led to permanent discontinuation of the study drug, as stated above.

Clinical laboratory evaluations

No clinically meaningful findings were detected in the mean baseline hematology parameters or in the mean changes from baseline following the initiation of administration of BRV to the last value recorded in the Evaluation Period in participants <18 years of age.

There were 2 participants reporting TEAEs associated with hematological parameters: anaemia (1 subject), decreased white blood cell, monocyte and neutrophil counts in one (14.3%) subject. The latter TEAE was considered drug-related by the Investigator. Haematological parameters were not associated with SAEs or permanent discontinuation of the study drug.

There were no meaningful findings reported as TEAEs in the baseline blood chemistry parameters by Baseline mean values or in the mean changes from Baseline to the last value recorded in the Evaluation Period. Possibly clinically significant treatment-emergent abnormalities post-baseline were reported in 1 study participant (14.3%) each: high alanine aminotransferase, high protein, high cholesterol, high LDL cholesterol, high triglycerides, and impaired glucose tolerance. These were not considered drug-related or serious, and they did not lead to permanent discontinuation of the study drug. In urinalysis, there were no relevant baseline findings, and possibly clinically significant treatment-emergent abnormalities were reported as follows: in two subjects (28.6%) ketone values, one subject (14.3%) protein values, and two urinary tract infections were reported by one participant. All TEAEs were of mild intensity and not considered serious or as related to the study drug.

Vital signs, physical examination and ECG findings

There were possibly clinically significant treatment-emergent abnormalities in diastolic blood pressure in 4 participants: low in one (14.3%) subject, high in three (42.9%) subjects. Heart rate values were high in three (42.9%) subjects. No significant ECG abnormalities were recorded during the study.

Possibly clinically significant body weight values were common as judged by the age group-specific weight criteria (<3% or >97% of body weight growth curve ranges): post-baseline had 2 participants (28.6%) low body weight and 5 participants (71.4%) high body weight. Possibly clinically significant treatment-emergent values were observed as soon as 2 months after Visit 1 and as late as 10 years after. Actual TEAEs were reported in one subject (14.3%) each: weight decreased and weight increased, and these were considered drug-related by the Investigator. No TEAEs related to vital signs led to permanent discontinuation of study drug nor were they considered treatment-emergent SAEs.

Assessor's comment

Of the primary SOCs of TEAEs, psychiatric and gastrointestinal disorders as well as TEAEs deemed severe have a seemingly higher representation by percentage among the patients <18 years of age in comparison with the adult population of the study N01125. However, considering the special characteristics of the cohort (adolescents, high relative proportion of ULD patients) and especially its minute size with a very high degree of contingency, the results are regarded as being in line with the overall study population.

2.3.3. Discussion on clinical aspects

A total of 7 patients ≤18 years old were included in study N01125, which comprises approximately 0.82 % of the total study population (n=853 patients). It is challenging to compare the study results between children and adults not least given the very limited number of children; however, the outcome for the patients in the age range 16-18 seems consistent with the result of the overall study population.

All patients reported TEAEs (7 subjects; 100 %). One event in a series of events led to permanent discontinuation of study drug in one subject (14.4%). In the paediatric population, 4 (57.1%) of the TEAEs were deemed severe. There were 3 (42.9%) treatment-emergent SAEs in the paediatric group, unrelated to treatment. All reported frequencies are reasonably consistent and in line with the reported frequencies in the overall population.

The safety profile of brivaracetam in the paediatric population is currently reflected in the SmPC. No new safety concerns were identified, and consequently, there is no need to update the product information based on this limited dataset.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of N01125 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 limited number and the character of the reported TEAEs in subjects ≤18 years of age does not raise new safety 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.