EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/370511/2018
Human Medicines Evaluation 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/P46/002

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Table of contents

1. Introduction

On 16 March 2018, The MAH submitted the results of N01199 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation), which requires UCB to submit information on studies conducted in children (<18 years of age) treated with brivaracetam (BRV; BRIVIACT®, [NUBRIVEO in Italy] (2S)-2-[(4R)-2-oxo-4-propyltetrahydro-1H-pyrrol-1-yl]butanamide).

An abbreviated clinical study report (CSR) based on a clinical cutoff date of 17 Jan 2014 was previously submitted for N01199 for the purpose of providing supportive information for the BRV partial-onset seizures (POS) adjunctive therapy Marketing Authorization Application (MAA) submission (Sequence 0000, Module 5 Section 5.3.5.2). The current report is the final CSR based on the completed study.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that “N01199 is a phase 3, therapeutic, multicenter, noncomparative, open-label, single-arm, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of brivaracetam (BRV) used at individualized doses with a maximum of 200mg/day in subjects aged 16 years or older diagnosed with epilepsy” is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

The investigational medicinal product (IMP; BRV tablets) was supplied oral tablets of BRV 2.5mg, 10mg and 25mg. Initially, BRV 2.5mg and 10mg tablets were packaged in blister cards containing 20 tablets each. Visit cartons of 80 (4 blister cards) and 200 (10 blister cards) tablets were provided and each visit carton had a unique, pre-printed identification number. In Nov 2006, a transition from blister cards to HDPE bottles was implemented. Brivaracetam 2.5mg tablets were packaged in bottles of 200 tablets and BRV 10mg tablets were packaged in bottles of 80 and 200 tablets. Each bottle had a unique, pre-printed identification number. HDPE bottles containing 80 and 200 tablets of BRV 25mg were made available when subjects began enrolling from BRV Phase 3 studies (N01252, N01253, and N01254). Protocol Amendment 6 (26 Jun 2011) included the progressive removal of 2.5mg tablets and containers of 80 tablets.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- A phase 3, therapeutic, multicenter, non-comparative, open-label, single-arm, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of brivaracetam (BRV) used at individualized doses with a maximum of 200mg/day in subjects aged 16 years or older diagnosed with epilepsy (N01199);

2.3.2. Clinical study

A phase 3, therapeutic, multicenter, non-comparative, open-label, single-arm, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of brivaracetam (BRV)

used at individualized doses with a maximum of 200mg/day in subjects aged 16 years or older diagnosed with epilepsy (N01199)

Description

N01199 was a Phase 3, therapeutic, multicenter, noncomparative, open-label, single-arm, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of BRV used at individualized doses with a maximum of 200mg/day in subjects aged 16 years or older diagnosed with epilepsy.

This study included 30 patients of 16 and < 18 years old.

Methods

Objective(s)

In N01199, the primary objective was to evaluate the long-term safety and tolerability of BRV at individualized doses with a maximum of 200mg/day in subjects suffering from epilepsy. The secondary objective was to evaluate the maintenance of efficacy over time of BRV (for POS/primary generalized seizure [PGS] subjects).

Study design

N01199 was a Phase 3, therapeutic, multicenter, noncomparative, open-label, single-arm, long-term follow-up (LTFU) study to evaluate long-term safety and efficacy of BRV used at individualized doses with a maximum of 200mg/day in subjects aged 16 years or older diagnosed with epilepsy.

Study population /Sample size

N01199 enrolled subjects 16 years of age and older who had completed N01193, N01252, N01253, or N01254. Subjects from N01252 and N01254 enrolled into LTFU studies, either N01125 or N01199, depending on their country of residence. N01193, N01252, and N01253 enrolled subjects with POS with or without secondary generalization (designated as “subjects with POS”). Study N01254 enrolled subjects with POS and also a smaller number of subjects with generalized epilepsy. Of note, no subjects <18 years of age with PGS were enrolled in N01199.

Subjects from the double-blind, placebo-controlled study, N01193, entered N01199 at a dose of BRV 20mg/day. Subjects from the double-blind, placebo-controlled study N01252 entered N01199 at a dose of BRV 50mg/day. Subjects from the double-blind, placebo-controlled study N01253 entered N01199 at a dose of BRV 50mg/day or 20mg/day. The starting doses for subjects from the double-blind, placebo-controlled, flexible-dose study N01254 were based on the blinded dose levels achieved during the Maintenance Period of N01254, but were not to exceed BRV 100mg/day; thus, starting doses for subjects from N01254 were BRV 20mg/day, 50mg/day, or 100mg/day, with most subjects entering N01199 at a dose of BRV 100mg/day.

Subjects who enrolled in the study directly entered the Evaluation Period. The dose of BRV could have been adjusted based on the individual subject’s seizure control and tolerability. Brivaracetam dose increases could have been made in increments of a maximum of 50mg/day on a weekly basis up to a maximum of 200mg/day. Likewise, dose decreases could be made by steps of maximum BRV 50mg/day on a weekly basis. Of note, N01199 started with a maximum dose of BRV 100mg/day; however, the protocol was amended to allow for a maximum dose of BRV 150mg/day (Protocol Amendment 2, 02 Mar 2007) and subsequently for a maximum dose of BRV 200mg/day (Protocol Amendment 6, 26 Jun 2011) in subjects with epilepsy.

Subjects who discontinued treatment with BRV entered a Down-Titration Period during which 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.

Subjects who completed the Down-Titration Period or subjects who discontinued during the Evaluation Period without entering 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.

The maximum allowable daily dose for this study was increased from BRV 150mg/day to 200mg/day based on Protocol Amendment 6 (26 Jun 2011). It was recommended that the daily dose be administered in 2 equal intakes.

Dose adjustment to concomitant antiepileptic drugs (AEDs) may have been made at any time during the study and subjects 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 subject receiving BRV monotherapy. Before Protocol Amendment 6, 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 Protocol Amendment 6, conversion to monotherapy was no longer permitted; however, subjects already on BRV monotherapy were allowed to continue monotherapy treatment.

This study ran for the duration of the clinical development period of BRV, and continued until a marketing authorization was granted by any Health Authority in an indication of the adjunctive treatment in adults with refractory POS, whether or not secondarily generalized, until the Sponsor closed the study, until subjects transitioned to another BRV 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 subject was variable; the maximum study duration was 11 years.

Treatments

In N01199, subjects coming from previous BRV studies had the opportunity to access BRV treatment at a flexible dose up to a maximum of 200mg/day in twice daily administration. The maximum allowable daily dose of BRV was increased from 100mg/day to 150mg/day based on Protocol Amendment 2 (02 Mar 2007); subsequently, the maximum allowable daily dose of BRV was increased from 150mg/day to 200mg/day based on Protocol Amendment 6 (26 Jun 2011). It was recommended that the daily BRV dose be divided equally, taken with or without food, and that the first intake would have been in the evening of the day of the dispensation of the study medication.

The individual starting dose for each subject was the dose defined/reached at the end of their respective previous study. Dose changes were made in even increments (for example, BRV 20mg, BRV 30mg, or BRV 40mg) with the implementation of the IVRS/ IWRS.

At each visit in N01199, if necessary, the dosage could have been adapted as follows:

- Up-titration could be made by increments of maximum BRV 50mg/day on a weekly basis, up to a maximum dose of BRV 200mg/day.
- Dose decreases could be made by steps of maximum BRV 50mg/day on a weekly basis, with a last down-titration step at BRV 20mg/day for 1 week prior to the study drug-free period.

In case a subject did not continue with the study drug, the Investigator planned the progressive down-titration of the study drug (preferably at the EDV). The Down-Titration Period was to be followed by a period free of study drug for 2 to 4 weeks followed by the occurrence of the Final Visit.

Outcomes/endpoints

The primary safety variables of N01199 were as follows:

- Occurrence of a treatment-emergent adverse event (TEAE)
- Withdrawal due to adverse event (AE)
- Occurrence of a serious adverse event (SAE)

The secondary efficacy variables were as follows:

- POS (Type I) frequency per 28 days during the Evaluation Period Percent reduction in POS (Type I) frequency per 28 days from Baseline of the previous study to the Evaluation Period
- Responder rate for POS (Type I) frequency over the Evaluation Period. A responder was defined as a subject with a ≥50% reduction in seizure frequency from the Baseline Period of the previous study

Statistical Methods

Statistical analysis and generation of tables, figures, subject data listings, and statistical output was carried out using SAS version 9.1 or higher. Descriptive statistics, such as the mean, standard deviation (SD), median, 25th percentile, 75th percentile, minimum value, and maximum value for quantitative variables, and counts and percentages for categorical variables, were provided. Denominators for percentages were generally based on the set of subjects with at least 1 assessment at the time point or at least 1 assessment during the time interval being summarized.

All summaries were descriptive; no statistical hypothesis testing was planned.

Results

Recruitment/ Number analysed

The N01199 study was conducted over a total of 11 years and enrolled 668 patients. A total of 171 subjects (25.6%) completed the study. Overall, 497 subjects (74.4%) discontinued from the study.

In the N01199 study, a total of 30 subjects were <18 years of age. A total of 6 subjects (20.0%) <18 years of age completed the study. Overall, 24 subjects (80.0%) discontinued from the study. The most common reasons for discontinuation from the study for subjects with POS were the same as for the BRV overall population, and included AE, lack of efficacy, and subject choice (6 subjects [20.0%] each).

Baseline data

Thirty subjects were <18 years of age in the Safety Analysis Set. The mean age for all subjects was 16.6 years (ranging from 16 to 17 years). There were slightly more males (17 subjects [56.7%]) than females (13 subjects [43.3%]). The most common overall racial group was Asian (15 subjects [50%]) followed by White (11 subjects [36.7%]). Overall, mean weight and height were 56.1kg and 160.9cm,

respectively. Body mass index category was <18.5kg/m2 for 11 subjects (36.7%), between 18.5 to <25kg/m2 for 14 subjects (46.7%), between 25 to <30kg/m2 for 3 subjects (10.0%), and between 30 to <40kg/m2 for 2 subjects (6.7%).

Baseline epileptic characteristics

The mean duration of epilepsy for subjects <18 years of age was 10.3 years (ranging from 0 to 17 years) and the mean age at time of first seizure was 6.7 years (ranging from 0 to 17 years).

Subjects <18 years of age in the Efficacy Analysis Set reported partial seizures (30 subjects [100%]) at any time prior to study entry into the previous double-blind studies, including simple partial seizures (IA) (10 subjects [33.3%]), complex partial seizures (IB) (23 subjects [76.7%]), and partial evolving to secondary generalized seizures (IC) (15 subjects [50.0%]). No subjects <18 years of age reported generalized seizures prior to entry into the previous double-blind studies. All seizure types were determined per Investigator.

For subjects <18 years of age, the classification of epileptic syndrome at Baseline of the previous double-blind study was epileptic syndrome unknown for 2 subjects (6.7%). The remaining subjects had localization-related epileptic syndrome, the majority of which were symptomatic (17 subjects [56.7%]), followed by cryptogenic (7 subjects [23.3%]) and idiopathic (4 subjects [13.3%]).

At Baseline of the previous double-blind study in subjects <18 years of age, 14 subjects (46.7%) had known seizure focus localization. Of those, the most frequently reported seizure focus localization was temporal (8 subjects [26.7%]), followed by frontal (7 subjects [23.3%]), and parietal and occipital (2 subjects [6.7%] each).

The most frequently reported etiology in subjects <18 years of age was Unknown (14 subjects [46.7%]). Other reported etiologies were Congenital malformation (4 subjects [13.3%]), Perinatal events (Asphyxia during birth) (2 subjects [6.7%]), Cerebral infection (4 subjects [13.3%]), and Other (6 subjects [20.0%]).

Previous AEDs were AEDs taken within 5 years and discontinued prior to entry into the previous double-blind studies. The majority of subjects <18 years of age with POS had taken either 0 to 1 AED (16 subjects [53.3%]) or 2 to 4 AEDs (12 subjects [40.0%]); a total of 2 subjects had taken ≥5 AEDs (6.7%).

Overall, 30 subjects (100.0%) <18 years of age in the POS Efficacy Analysis Set were taking at least 1 AED at entry into the previous double-blind study. The most commonly reported AED was carbamazepine (17 subjects [56.7%]), followed by clobazam (7 subjects [23.3%]), topiramate (6 subjects [20.0%]), valproic acid (5 subjects [16.7%]), lamotrigine and oxcarbazepine (4 subjects [13.3%] each). All other AEDs taken at entry into the previous double-blind study were taken by ≤10% of subjects.

Efficacy results

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

- During the Evaluation Period, subjects reported a median (Q1, Q3) POS frequency of 9.1 seizures per 28-day period, ranging from 0 to 363 seizures, compared with Baseline median and mean (SD) POS frequency of 20.7 seizures and 29.1 (67.6) seizures, respectively.
- During the Evaluation Period, subjects reported a median (Q1, Q3) reduction in POS frequency from Baseline of 59.3% (3.3, 76.4) per 28-day period. The mean (SD) reduction in POS frequency during the Evaluation Period was 38.0% (55.1) per 28-day period. For subjects who

remained in the study and on BRV treatment, median percent reductions in POS frequency increased by exposure duration cohort from Baseline.

- The 50% responder rate for POS frequency during the Evaluation Period for subjects with POS was 56.7% (30 subjects). The 50% responder rate was increased within the first year and remained generally stable across the remaining cohorts.

Safety results

Extent of exposure

All subjects <18 years of age Safety Analysis Set (30 subjects [100%]) received at least 1 dose of BRV. Total subject-years of exposure was 127.4 years.

The most common modal dose of BRV was 150mg/day (12 subjects [40.0%]). A total of 8 subjects (26.7%) received a modal dose of 50mg/day, 6 subjects (20.01%) received a modal dose of 100mg/day, 2 subjects (6.7%) received a modal dose of 200mg/day, 1 subject (3.3% each) received a modal dose of 20mg/day and 5mg/day. No subjects received a modal dose of BRV >200mg/day.

No TEAEs were reported in the subjects who had a total daily dose of BRV >200mg/day during the time of overdosing.

Two subjects received a total daily dose of BRV <20mg/day. No TEAEs were reported in the subjects whose total daily dose was less than planned as described by the protocol. No subject received a total daily dose <5mg/day.

Approximately half of the subjects (14 subjects [46.7%]) had at least 42 months of exposure to BRV; and more than 25% completed at least 96 months of treatment.

Adverse events

A total of 24 subjects <18 years of age reported at least 1 TEAE (80.0% [229 events]); of these, 5 subjects reported a treatment-emergent SAE (16.7% [15 events]). A total of 13 subjects reported a TEAE that was considered by the Investigator to be drug-related (43.3% [76 events]), and 2 subjects reported a treatment-emergent SAE that was considered by the Investigator to be drug-related (6.7% [3 events]). Overall, 6 subjects discontinued the study due to TEAEs (20.0% [7 events]) and 6 subjects reported severe TEAEs (20.0% [20 events]). Three subjects (10.0%) reported a TEAE of pregnancy leading to permanent discontinuation of study drug; none were assessed by the Investigator as drug-related. Other TEAEs leading to permanent discontinuation of study drug included toxicity to various agents, dizziness, abnormal behavior, and schizophrenia (1 subject [3.3%] each).

No deaths were reported during the study for subjects <18 years of age.

The most commonly reported TEAEs by PT in subjects <18 years of age were headache (8 subjects [26.7%]), pyrexia (7 subjects [23.3%]), and decreased appetite (5 subjects [16.7%]). Other commonly reported TEAEs included upper respiratory tract infection, weight decreased, dizziness, convulsion, and cough (4 subjects [13.3%]). All other TEAEs occurred in ≤3 subjects.

For subjects <18 years of age the incidence of TEAEs was highest during the first 3-month safety time interval, and was lower and relatively stable at all subsequent safety time intervals.

Most subjects <18 years of age reported TEAEs with a maximum intensity of moderate (15 subjects [50.0%]). A total of 3 subjects (10.0%) and 6 subjects (20.0%) experienced TEAEs with a maximum intensity of mild or severe, respectively. Severe TEAEs were most frequently reported in the General Disorders and Administration Site Conditions and Infections and Infestations System Organ Class

(SOC) (6.7% each); the most frequently reported severe TEAE was pyrexia and pregnancy (2 subjects [6.7%] each).

Overall in subjects <18 years of age, 5 subjects (16.7%) reported 5 TEAEs potentially associated with seizure worsening. All of these events occurred within the SOC of Nervous system disorders, the reported TEAEs potentially associated with seizure were convulsion (4 subjects [13.3%]) and epilepsy (1 subject [3.3%]) and no subjects reported TEAEs leading to permanent discontinuation of study drug.

Overall in subjects <18 years of age, 6 subjects (20.0%) reported 6 TEAEs potentially associated with behavioral disorders. The most commonly reported TEAE potentially associated with behavioral disorders was irritability (3 subjects [10.0%]), followed by abnormal behavior, aggression, and obsessive-compulsive disorder (1 subject [3.3%] each). For TEAEs evaluated per safety time interval, 3 subjects (10.0%) reported TEAEs potentially associated with behavioral disorders during the first 3 months of the study.

No subjects <18 years of age reported TEAEs potentially associated with cognitive impairment.

Overall in subjects <18 years of age, 4 subjects (13.3%) reported 4 TEAEs potentially associated with suicidality or suicidal ideation. The reported TEAEs potentially associated with suicidality or suicidal ideation included laceration (2 subjects [6.7%]), depression and toxicity to various agents (1 subject [3.3%], each). Of the 4 subjects who reported TEAEs potentially associated with suicidality or suicidal ideation, 3 subjects reported TEAEs that were assessed by the Investigator as drug-related (laceration, depression, and toxicity to various agents), no subject reported a severe TEAE, no subject reported SAEs, and no subject reported TEAEs leading to permanent discontinuation of study drug.

Overall in subjects <18 years of age, 2 subjects (6.7%) reported TEAEs potentially associated with hepatotoxicity. The reported TEAEs potentially associated with hepatotoxicity were alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased, and hyperammonaemia (1 subject [3.3%]), and liver function test abnormal, (1 subject [3.3%]).

Of the 2 subjects who reported TEAEs potentially associated with hepatotoxicity, 1 subject reported a TEAE that was assessed by the Investigator as drug-related, severe in intensity and serious (hyperammonaemia), and none of these subjects reported TEAEs leading to permanent discontinuation of study drug.

Overall in subjects <18 years of age, 10 subjects (33.3%) reported 12 TEAEs potentially associated with abuse potential. The TEAEs reported by ≥5% of subjects which were potentially associated with abuse potential were dizziness (4 subjects [13.3%]), somnolence and fatigue (2 subjects [6.7%] each). All other TEAEs potentially associated with abuse potential were reported by 1 subject each. Of note, the TEAEs of dizziness, somnolence, and fatigue are commonly observed in AEDs including BRV.

Of the 10 subjects who reported TEAEs potentially associated with abuse potential, the majority (7 TEAEs) were assessed by the Investigator as drug-related.

No subject reported a severe TEAE, 1 subject reported 2 SAEs potentially associated with abuse (toxicity to various agents and abnormal behavior), and 2 subjects reported TEAEs leading to permanent discontinuation of study drug (toxicity to various agents and dizziness).

Overall in subjects <18 years of age, 3 pregnancies (10.0%) were reported. One of the 3 pregnancies occurred in a subject who was on non-oral hormonal contraceptive. All 3 pregnancies resolved in the births of live babies.

There were no clinically meaningful findings in the mean Baseline hematology parameters or in the mean changes from Baseline to the last value recorded in the Evaluation Period in subjects <18 years of age. Three subjects (10.0%) had high and 3 subjects had low post-Baseline PCST eosinophil values, 2 subjects (6.7%) had high post-Baseline PCST basophils/leukocyte values, and 2 subjects (6.7%) had low hemoglobin values. Overall in subjects <18 years of age, there were 3 subjects who reported 7 TEAEs associated with abnormalities in hematology parameters. The most frequently reported TEAE was mean cell volume increased (2 subjects [6.7%]). All TEAEs associated with abnormalities in hematology parameters were considered drug-related by the Investigator.

In subjects <18 years of age, there were no clinically meaningful findings 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. Four subjects (13.3%) had post-Baseline PCST high gamma-glutamyl transferase values, 2 subjects (6.7%) each had post-Baseline PCST high alanine aminotransferase values, alkaline phosphatase values, aspartate aminotransferase values, and protein values. Overall in subjects <18 years of age, all 8 TEAEs related to abnormalities in blood chemistry parameters were reported by 1 subject. These events included gamma-glutamyltransferase increased, blood triglycerides increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, and blood potassium increased. One TEAE was considered by the Investigator to be drug-related (blood triglycerides increased).

Baseline urinalysis parameters were generally within normal ranges and there were no mean changes from Baseline to the Last Value during the Evaluation Period considered clinically relevant. Two subjects (6.7%) had post-Baseline PCST ketone values, 1 subject (3.3%), each had post-Baseline PCST protein values and glucose values, and no subjects had post-Baseline PCST leukocytes values.

There were no clinically meaningful findings in vital sign parameters or body weight over time or in the mean changes from Baseline to the Last Value recorded in the Evaluation Period. The overall incidence of PCST body weight values was 63.3%. Thirteen subjects (43.3%) had post-Baseline PCST high body weight, 10 subjects (33.3%) had post-Baseline PCST low body weight. A total of 2 subjects (6.7%) had post-Baseline PCST high SBP values, and 3 subjects (10.0%) had post-Baseline PCST low DBP values. The most commonly reported TEAEs related to vital signs and body weight included weight decreased (4 subjects [13.3%]), and weight increased (2 subjects [6.7%]).

One subject <18 years of age had abnormal clinically significant ECG findings at Baseline and no other clinically significant ECG finding thereafter.

2.3.3. Discussion on clinical aspects

30 patients <18 years old were included into the N01199 study, which comprises approximately 4.5% of total study population (n=668). Similar number of <18 years old patients completed the study as all population of the study. More <18 years old patients (53%) were treated with 0-1 AEDs compared to all patients in the N01199 study (45%) or patient population in pivotal studies (25%; Pool E1). Slightly less than half of the <18 years old patients (n=14; 47%) had at least 42 months exposure which was similar to all patient population in the N01199 study (n=347; 52%). Even though the primary focus of the study was long-term safety it should be noted that the 50% responder rate for POS frequency during the Evaluation Period for subjects with POS was 56.7% (30 subjects), which was similar to the 50% responder rate for the all subjects in N01199 study (56%).

The overall safety profile was similar to that reported for BRV administered as adjunctive therapy in other long-term, open-label studies and no new safety concerns were identified in <18 years old patients.

Based on this limited size data set (n=30) it could be concluded that long-term treatment with BRV at doses up to 200mg/day, when used as adjunctive therapy in subjects with POS was generally well tolerated in <18 years old patients. However, due to small number of patients the results for subjects <18 years of age should be interpreted with caution.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted the results of N01199 in accordance with Article 46 of Regulation (EC) No 1901/2006 (The Paediatric Regulation). The limited number and character of the reported TEAEs in subjects <18 years of age treated with brivaracetam in the study N01199 does not raise new safety concerns. The MAH does not propose any changes of the currently approved SmPC based on the presented data, which is supported.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**