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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: EMA/PAM/0000265372

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
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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1. Introduction

On 7 April 2025, the MAH submitted a completed paediatric study 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 EP0099 study - A NONINTERVENTIONAL PROSPECTIVE STUDY OF BRIVARACETAM UTILIZATION AND EFFECTIVENESS AS AN ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL-ONSET SEIZURES IN STANDARD MEDICAL PRACTICE IN A MULTINATIONAL SETTING is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Brivaracetam was prescribed according to routine clinical practice and in accordance with the approved SmPC.

CHMP comment

No information was provided regarding the specific formulations of brivaracetam used by paediatric patients in this study.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- The EP0099 study - A NONINTERVENTIONAL PROSPECTIVE STUDY OF BRIVARACETAM UTILIZATION AND EFFECTIVENESS AS AN ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL-ONSET SEIZURES IN STANDARD MEDICAL PRACTICE IN A MULTINATIONAL SETTING;

2.3.2. Clinical study

EP0099 - A NONINTERVENTIONAL PROSPECTIVE STUDY OF BRIVARACETAM UTILIZATION AND EFFECTIVENESS AS AN ADJUNCTIVE THERAPY IN THE TREATMENT OF PARTIAL-ONSET SEIZURES IN STANDARD MEDICAL PRACTICE IN A MULTINATIONAL SETTING

Description

The EP0099 NIS (BRIVA-REG), was a post marketing, multinational, observational, prospective NIS with a 12 month Observation Period designed to explore long term utilization, effectiveness, and safety and tolerability of adjunctive brivaracetam treatment for POS in adults and paediatric patients 4 to <18 years.

EP0099 was conducted in mid-European countries (Bulgaria, Czech Republic, Greece, Hungary, Poland, and Romania). Study sites offered sequential enrollment in EP0099 to all eligible patients, as per the study selection criteria (see EP0099 study report Section 9.3.1).

After the Baseline Visit (Visit 1/Day 1 of brivaracetam treatment) each patient was followed up for approximately 12 months. The type (physical or remote consultation) and frequency of medical visits and all evaluations were performed as per routine clinical practice, resulting in a total of approximately 3 post Baseline visits, as follows:

- Visit 1, Baseline, Day 1: represented the first day of brivaracetam treatment
- Visit 2, approximately 3 months after Baseline
- Visit 3, approximately 6 months after Baseline
- Visit 4, approximately 12 months after Baseline or EOS

Should a patient have seen the physician more than once within the same visit time window, all clinical data were collected. No clinical diagnostic or monitoring procedures were applied, except as required in the standard practice of medicine, and patients did not undergo any procedures or assessments that deviated from the standard clinical routine in the participating countries and/or sites, apart from asking to complete patient questionnaires (which were fully voluntary).

The study ended for each patient after approximately 12 months, with the last planned visit per clinical routine. Patients who discontinued brivaracetam prior to the end of the study's 12 month Observation Period were asked to continue to be observed until 12 months had elapsed since enrollment.

The Helpilepsy platform (www.helpilepsy.com), a mobile application for patients and a web based dashboard for physicians, was used for patient questionnaires in EP0099. PRO questionnaires intended for pediatric patients (≥8 to <18 years of age at Baseline), PedsQL and the Pediatric Cognitive Function Neuro-QoL SF, were completed within the Helpilepsy application. If the patient chose to not use or could not use the Helpilepsy application, these data were not collected (no paper PRO questionnaires were provided).

Methods

Study participants

The following selection criteria must have been fulfilled for patients entering the NIS:

1. 1. The patient had never been treated with brivaracetam prior to Baseline/Visit 1.
2. 2. The patient was ≥4 years of age.
3. 3. The decision by the treating physician to prescribe brivaracetam was made independently from participation in the NIS.
4. 4. The patient met the criteria for treatment with brivaracetam as adjunctive therapy (≥1 concomitant AED) according to the current SmPC in Europe.
5. 5. The patient had a clinical diagnosis of epilepsy with POS with or without secondary generalization.
6. 6. Clinical data for 3 months prior to brivaracetam initiation were available.
7. 7. The patient was willing to be followed for a 12-month period.

CHMP comment

The paediatric patients were only a part of patients' population included into the study. It is noted that only patients ≥ 4years old were included into the study despite the indication allowing treatment of POS in patients from 2 years old.

Treatments

Brivaracetam was prescribed according to routine clinical practice and in accordance with the approved SmPC, current at the time of enrollment in Europe. The prescription of brivaracetam was clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures were performed.

Patients who initiated brivaracetam adjunctive therapy either added to an existing AED or replaced another AED therapy in standard medical practice. The patients were followed as per current clinical practice.

Objective(s)

The primary objective of the study was to assess the overall effectiveness of brivaracetam add-on therapy through brivaracetam retention in patients with POS 12 months after brivaracetam treatment initiation. The secondary objectives of the study were: 1) to assess overall effectiveness of brivaracetam add-on therapy through brivaracetam retention at specified time points (3 and 6 months) after brivaracetam treatment initiation; and 2) to assess overall effectiveness of brivaracetam add-on therapy in reducing seizures at specified time points (3, 6, and 12 months) after brivaracetam treatment initiation. Other objectives of the study were: 1) to assess the safety and tolerability profile of patients with brivaracetam administration in a real-life setting; 2) to assess the change in overall health outcomes measures (patient and clinician reported) after brivaracetam initiation for patients on brivaracetam and for patients who had discontinued brivaracetam; 3) to describe utilization of brivaracetam including but not limited to demographic and disease characteristics of specific patient populations; and 4) to explore Baseline and treatment factors associated with brivaracetam effectiveness.

CHMP comments

The main objective of the study was to evaluate retention of brivaracetam treatment for 12 months as well as it's effectiveness at specific timepoints when used according to approved indication.

Outcomes/endpoints

The primary variable of the study was brivaracetam retention at 12 months.

The secondary variables were:

• Brivaracetam retention at 3 and 6 months

For patients still on brivaracetam:

- Seizure freedom (all seizure types) at 3, 6, and 12 months
- POS frequency (seizures per 28 days) at Baseline, 3, 6, and 12 months and percent change in POS frequency from Baseline to each visit
- Response based on percent change in POS frequency at 3, 6, and 12 months (response was defined as a reduction of ≥50% from Baseline)

The safety variables were:
• Incidence of TEAEs (overall; serious; drug-related; leading to discontinuation of brivaracetam)
• Incidence of behavioral TEAEs (overall; serious; drug-related; leading to discontinuation of

brivaracetam)
- Incidence of AESI
- Incidence of prior AEs (at Baseline) that lead to discontinuation of prior AEDs
- Incidence of other safety relevant information

The health outcome variables were:

- CGIC at 3, 6, and 12 months

Scores and CFB at each visit (3, 6, and 12 months) for the following:

- PedsQL scores (for patients ≥8 to <18 years of age at Baseline)

- Pediatric Cognitive Function Neuro-QoL SF scores (for patients ≥8 to <18 years of age at

Baseline)

Sample size

EP0099 planned to enroll approximately 900 patients at least 4 years of age who had a confirmed history of POS (ie, ILAE 2017 classification, focal onset seizures [Fisher et al, 2017]).

CHMP comment

It is noted that no specific goal for paediatric patients enrolment was set.

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

The all patient documented (APD) Set was defined as all patients included in the study with valid data consent and for whom at least Visit 1 (Baseline) was documented. The APD Set was used for patient disposition and patient data listings only.

The SS was defined as all patients included in the APD Set who had received at least 1 dose of treatment with brivaracetam while in the study. The SS was used for the analysis of all study variables, not including analyses for the subgroups female, age group, number of lifetime AEDs, number of concomitant AEDs, and selected comorbidities.

The PPS was defined as all patients in the SS who were treated according to the approved SmPC during their Observation Period, representing the on-label use of brivaracetam in Europe.

Descriptive statistics were displayed to provide an overview of the study results; there were no inferential analyses. CIs were also provided for selected variables for information purposes only. For continuous variables, descriptive statistics included number of patients with available measurements (n), mean, SD, minimum, median, maximum, 25% and 75% quartiles, and interquartile range. Categorical variables were summarized by the number and percentage of patients in each category.

Results

Participant flow

Recruitment

The APD Set consisted of 56 enrolled paediatric patients with valid data consent and with at least the Baseline visit documented. The SS consisted of 56 paediatric patients (100%) who were included in the APD Set and received at least 1 dose of brivaracetam while in the study. The PPS consisted of 28 paediatric patients (50.0%) who were included in the SS who did not have any important protocol

deviations and were prescribed brivaracetam according to the approved SmPC, current at the time of enrollment in Europe.

CHMP comment

It is noted that out of 798 totally recruited patients there were 56 paediatric patients (7%).

Baseline data

In the SS, at Baseline, the mean (SD) age of paediatric patients was 11.9 (4.2) years. The majority of paediatric patients (51.8%) were 13 to <18 years of age and male (57.1%). The demographic and Baseline characteristics were generally similar between the SS and PPS (table below).

In the SS, paediatric patients were mainly enrolled from sites located in Romania (16 patients), Hungary (13 patients), and Greece (13 patients), and only a few paediatric patients were from Bulgaria (6 patients), Czech Republic (5 patients), and Poland (3 patients).

Table 1: Demographics and Baseline characteristics in paediatric patients (SS and PPS)

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
Age at Visit 1 (years)	Mean (SD)	11.9 (4.2)	12.0 (4.4)
	Median (Q1, Q3)	13.0 (8, 16)	12.5 (9, 16)
	IQR	8.0	7.5
	Min, Max	4, 17	5, 17
Age category at Visit 1 (years)			
4 to <18 years	n (%)	56 (100)	28 (100)
4 to <8 years	n (%)	12 (21.4)	6 (21.4)
8 to <13 years	n (%)	15 (26.8)	8 (28.6)
13 to <18 years	n (%)	29 (51.8)	14 (50.0)
Gender			
Male	n (%)	32 (57.1)	16 (57.1)
Female	n (%)	24 (42.9)	12 (42.9)
Education			
Not yet eligible for school	n (%)	8 (14.3)	3 (10.7)
Still in school	n (%)	46 (82.1)	23 (82.1)
Less than high school	n (%)	1 (1.8)	1 (3.6)
High school graduate	n (%)	1 (1.8)	1 (3.6)
Some college, no degree	n (%)	0	0
College degree	n (%)	0	0
Postgraduate or professional degree	n (%)	0	0

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
Current professional status			
Full time employed	n (%)	0	0
Part time employed	n (%)	0	0
Unemployed	n (%)	16 (28.6)	6 (21.4)
Not applicable	n (%)	40 (71.4)	22 (78.6)
Part time/unemployed reason			
Epilepsy	n (%)	1 (1.8)	1 (3.6)
Retired	n (%)	0	0
Seeking work	n (%)	0	0
House keeping	n (%)	0	0
Full-time student	n (%)	13 (23.2)	9 (32.1)
Part-time student	n (%)	0	0
Too young for employment	n (%)	36 (64.3)	16 (57.1)
Other	n (%)	2 (3.6)	1 (3.6)
Missing	n (%)	4 (7.1)	1 (3.6)
Helpilepsy User			
Yes	n (%)	18 (32.1)	9 (32.1)
No	n (%)	38 (67.9)	19 (67.9)

IQR=interquartile range; max=maximum; min=minimum; PPS=Per-Protocol Set; Q1=25th percentile; Q3=75th percentile; SD=standard deviation; SS=Safety Set
Note: Percentages were based on the number of patients in the SS or PPS.
Note: Helpilepsy user=Yes at Baseline or if no at Baseline but provided Helpilepsy data during the study.
Source: EP0099 Table 2.1.2P, EP0099 Table 2.1.3P

In the SS, 56 paediatric patients (100%) reported any medical history condition (including COVID 19 infection and epilepsy). The top 3 most frequently reported medical history conditions, by SOC, were Nervous system disorders (56 patients [100%]), Congenital, familial and genetic disorders (15 patients [26.8%]), and Psychiatric disorders (4 patients [7.1%]). Other than epilepsy, the most frequently reported medical history conditions, by PT, were mental retardation (6 patients [10.7%]), cerebral palsy (5 patients [8.9%]), and developmental delay (3 patients [5.4%]); all other PTs were reported by ≤2 patients.

In the SS, the median time since first diagnosis of epilepsy in paediatric patients was 7.23 years, and 11 patients (19.6%) had >10 years elapsed since their first diagnosis of epilepsy. The median percentage of life with epilepsy was 64.22%. The history of epilepsy was similar between the SS and PPS (table below).

Table 2: History of epilepsy in paediatric patients (SS and PPS)

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
Time since first diagnosis of epilepsy (years)	n	56	28
	Mean (SD)	6.83 (4.42)	7.08 (4.58)
	Median (Q1, Q3)	7.23 (3.20, 9.86)	7.70 (3.37, 10.04)
	IQR	6.66	6.67
	Min, max	0.3, 17.0	0.3, 16.9
Time since first diagnosis of epilepsy	n	56	28
0 to <1 year	n (%)	6 (10.7)	4 (14.3)
1 to <5 years	n (%)	16 (28.6)	7 (25.0)
5 to 10 years	n (%)	23 (41.1)	10 (35.7)
>10 years	n (%)	11 (19.6)	7 (25.0)
Age at the time of first diagnosis of epilepsy (years)	n	56	28
	Mean (SD)	5.08 (4.66)	4.89 (4.86)
	Median (Q1, Q3)	4.15 (1.12, 7.63)	3.57 (1.40, 7.11)
	IQR	6.51	5.71
	Min, max	0.0, 16.3	0.0, 16.3
Percent of life with epilepsy (%)	n	56	28
	Mean (SD)	59.10 (32.05)	61.10 (32.61)
	Median (Q1, Q3)	64.22 (35.98, 86.93)	67.60 (40.70, 84.83)
	IQR	50.95	44.13
	Min, max	1.9, 100.0	1.9, 100.0

IQR=interquartile range; max=maximum; min=minimum; PPS=Per-Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set

Note: Percentages were based on the number of patients in the SS or PPS.

Source: EP0099 Table 2.2.1P, EP0099 Table 2.2.2P

In the SS, 55 patients (98.2%) reported any Baseline seizures (based on the seizure counts collected for 3 months prior to the Baseline visit). A total of 50 patients (89.3%) reported any Baseline POS, and 6 patients (10.7%) reported none. Of the patients who reported any Baseline POS, the median (Q1, Q3) 28 day Baseline POS frequency was 3.33 (0.67, 10.00). A total of 20 patients (35.7%) reported any Baseline POS with secondary generalization, and 36 patients (64.3%) reported none. Of the patients who reported any Baseline POS with secondary generalization, the median (Q1, Q3) 28 day Baseline POS with secondary generalization frequency was 0.67 (0.33, 3.50). Baseline seizure frequencies were generally similar between the SS and PPS (table below).

Table 3: Baseline seizure frequency in paediatric patients (SS and PPS)

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
Any Baseline seizures	n	56	28
Yes	n (%)	55 (98.2)	28 (100)
No	n (%)	1 (1.8)	0
If yes, 28-day Baseline all types of seizure frequency [a]	n	55	28
	Mean (SD)	22.04 (56.64)	27.25 (56.23)
	Median (Q1, Q3)	3.33 (0.67, 10.00)	4.17 (0.67, 15.00)
	IQR	9.33	14.33
	Min, max	0.3, 300.0	0.3, 240.3
28-day Baseline all types of seizure frequency	n	56	28
0	n (%)	1 (1.8)	0
>0 to <1	n (%)	15 (26.8)	8 (28.6)
1 to 5	n (%)	19 (33.9)	7 (25.0)
>5 to 10	n (%)	9 (16.1)	4 (14.3)
>10	n (%)	12 (21.4)	9 (32.1)
Any Baseline POS	n	56	28
Yes	n (%)	50 (89.3)	25 (89.3)
No	n (%)	6 (10.7)	3 (10.7)
If yes, 28-day Baseline POS frequency [a]	n	50	25
	Mean (SD)	22.67 (56.09)	28.96 (59.15)
	Median (Q1, Q3)	3.33 (0.67, 10.00)	5.00 (0.67, 11.33)
	IQR	9.33	10.67
	Min, max	0.3, 266.7	0.3, 240.0
28-day Baseline POS frequency	n	56	28
0	n (%)	6 (10.7)	3 (10.7)
>0 to <1	n (%)	16 (28.6)	8 (28.6)
1 to 5	n (%)	14 (25.0)	5 (17.9)
>5 to 10	n (%)	10 (17.9)	5 (17.9)
>10	n (%)	10 (17.9)	7 (25.0)
Any Baseline POS with secondary generalization	n	56	28
Yes	n (%)	20 (35.7)	13 (46.4)

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
No	n (%)	36 (64.3)	15 (53.6)
If yes, 28-day Baseline POS with secondary generalization frequency [a]	n	20	13
	Mean (SD)	2.45 (3.17)	3.00 (3.70)
	Median (Q1, Q3)	0.67 (0.33, 3.50)	0.67 (0.33, 6.67)
	IQR	3.17	6.33
	Min, max	0.3, 11.0	0.3, 11.0
28-day Baseline POS with secondary generalization frequency	n	56	28
0	n (%)	36 (64.3)	15 (53.6)
>0 to <1	n (%)	11 (19.6)	7 (25.0)
1-5	n (%)	5 (8.9)	2 (7.1)
>5 to 10	n (%)	3 (5.4)	3 (10.7)
>10	n (%)	1 (1.8)	1 (3.6)
Any Baseline of all type generalized onset seizures	n	56	28
Yes	n (%)	13 (23.2)	7 (25.0)
No	n (%)	43 (76.8)	21 (75.0)
If yes, 28-day Baseline generalized onset seizure frequency [a]	n	13	7
	Mean (SD)	6.05 (11.53)	5.57 (11.02)
	Median (Q1, Q3)	0.67 (0.33, 3.33)	0.33 (0.33, 6.67)
	IQR	3.00	6.33
	Min, max	0.3, 33.3	0.3, 30.0

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
28-day Baseline generalized onset seizure frequency	n	56	28
0	n (%)	43 (76.8)	21 (75.0)
>0 to <1	n (%)	7 (12.5)	4 (14.3)
1 to 5	n (%)	3 (5.4)	1 (3.6)
>5 to 10	n (%)	1 (1.8)	1 (3.6)
>10	n (%)	2 (3.6)	1 (3.6)

IQR=interquartile range; max=maximum; min=minimum; POS=partial-onset seizure; PPS=Per-Protocol Set; Q1=25th percentile; Q3=75th percentile; SD=standard deviation; SS=Safety Set

Note: Percentages were based on the total number of patients in the corresponding category.

[a] Baseline seizure frequency per 28 days was based on the seizure counts collected at Baseline for 3 months prior to Baseline visit.

Source: EP0099 Table 2.4.1P, EP0099 Table 2.4.2P

In the SS, 36 patients (64.3%) reported any prior AEDs. In the SS, the top 4 most commonly reported prior AEDs, by PT, were levetiracetam (26 patients [46.4%]), valproate (9 patients [16.1%]), and carbamazepine and topiramate (8 patients [14.3%] each). The most commonly reported prior AEDs were generally similar between the SS and PPS (table below).

In the SS, the median number (Q1, Q3) of prior AEDs reported was 2.0 (1.0, 3.0); the median number was the same for the PPS.

Table 4: Prior AEDs occurring in ≥5% of paediatric patients in the SS or PPS (SS and PPS)

WHODD Sep/2020 B3 update PT	All patients (SS) N=56 n (%)	All patients (PPS) N=28 n (%)
Any prior AED medications	36 (64.3)	17 (60.7)
Levetiracetam	26 (46.4)	10 (35.7)
Valproate	9 (16.1)	6 (21.4)
Carbamazepine	8 (14.3)	5 (17.9)
Topiramate	8 (14.3)	7 (25.0)
Benzodiazepine [a]	7 (12.5)	5 (17.9)
Lacosamide	5 (8.9)	5 (17.9)
Lamotrigine	5 (8.9)	2 (7.1)
Vigabatrin	3 (5.4)	1 (3.6)
Oxcarbazepine	2 (3.6)	2 (7.1)
Phenytoin	2 (3.6)	2 (7.1)
Rufinamide	2 (3.6)	2 (7.1)
Zonisamide	2 (3.6)	2 (7.1)

AED=anti-epileptic drug; BRV=brivaracetam; PPS=Per-Protocol Set; PT=preferred term; SAP=statistical analysis plan; SS=Safety Set; WHODD=World Health Organization Drug Dictionary
Note: Prior AEDs were defined as AEDs discontinued prior to the date of first BRV administration.
Note: AEDs with similar active substance were grouped and summarized together as per EP0099 SAP Section 6.1.4. Combination AEDs were not considered for grouping.
[a] Benzodiazepine AEDs included bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate.
Source: EP0099 Table 5.2.1P, EP0099 Table 5.2.2P

In the SS, 53 patients (94.6%) reported any concomitant AEDs at brivaracetam initiation. The top 3 most frequently reported concomitant AEDs at brivaracetam initiation, by PT, were valproate (24 patients [42.9%]), carbamazepine (16 patients [28.6%]), and benzodiazepine (13 patients [23.2%]. The most frequently reported concomitant AEDs at brivaracetam initiation were generally similar between the SS and PPS (table below).

In the SS, the median number (Q1, Q3) of concomitant AEDs at brivaracetam initiation was 2.0 (1.0, 3.0); the median number was the same for the PPS.

Table 5: Concomitant AEDs at BRV initiation in ≥5% of paediatric patients in the SS or PPS (SS and PPS)

WHODD SEP/2020 B3 update PT	All paediatric patients (SS) N=56 n (%)	All paediatric patients (PPS) N=28 n (%)
Any concomitant AED medications at BRV initiation	53 (94.6)	28 (100.0)
Valproate	24 (42.9)	10 (35.7)
Carbamazepine	16 (28.6)	7 (25.0)
Benzodiazepine [a]	13 (23.2)	7 (25.0)
Lamotrigine	10 (17.9)	7 (25.0)
Lacosamide	8 (14.3)	6 (21.4)
Oxcarbazepine	7 (12.5)	5 (17.9)
Topiramate	6 (10.7)	4 (14.3)
Levetiracetam	5 (8.9)	4 (14.3)
Phenobarbital	3 (5.4)	2 (7.1)

AED=anti-epileptic drug; BRV=brivaracetam; PPS=Per-Protocol Set; PT=preferred term; SAP=statistical analysis plan; SS=Safety Set; WHODD=World Health Organization Drug Dictionary

Note: The concomitant AEDs at BRV initiation were defined as AEDs being taken on the same day or ongoing at the day of first BRV administration.

Note: AEDs with similar active substance were grouped and summarized together as per EP0099 SAP Section 6.1.4. Combination AEDs were not considered for grouping.

[a] Benzodiazepine AEDs included bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate.

Source: EP0099 Table 5.3.3P, EP0099 Table 5.3.4P

In the SS, 53 patients (94.6%) reported any concomitant AEDs. The top 3 most frequently reported concomitant AEDs, by PT, were valproate (25 patients [44.6%]), carbamazepine (16 patients [28.6%]), and benzodiazepine (14 patients [25.0%]). The most frequently reported concomitant AEDs were generally similar between the SS and PPS (table below).

Table 6: Any concomitant AED medications in ≥5% of paediatric patients in the SS or PPS (SS and PPS)

WHODD SEP/2020 B3 update PT	All paediatric patients (SS) N=56 n (%)	All paediatric patients (PPS) N=28 n (%)
Any concomitant AED medications	53 (94.6)	28 (100.0)
Valproate	25 (44.6)	11 (39.3)
Carbamazepine	16 (28.6)	7 (25.0)
Benzodiazepine [a]	14 (25.0)	8 (28.6)
Lamotrigine	12 (21.4)	9 (32.1)
Lacosamide	9 (16.1)	7 (25.0)
Oxcarbazepine	7 (12.5)	5 (17.9)
Topiramate	6 (10.7)	4 (14.3)
Levetiracetam	5 (8.9)	4 (14.3)
Phenobarbital	3 (5.4)	2 (7.1)
Vigabatrin	3 (5.4)	2 (7.1)

AED=anti-epileptic drug; BRV=brivaracetam; PPS=Per-Protocol Set; PT=preferred term; SAP=statistical analysis plan; SS=Safety Set; WHODD=World Health Organization Drug Dictionary
Note: Concomitant AEDs were defined as AEDs taken at least 1 day in common with BRV.
Note: AEDs with similar active substance were grouped and summarized together as per EP0099 SAP Section 6.1.4. Combination AEDs were not considered for grouping.
[a] Benzodiazepine AEDs included bromazepam, alprazolam, cloxazolam, diazepam group, chlordiazepoxide, clonazepam, clobazam, lorazepam, clotiazepam, temazepam, and clorazepate.
Source: EP0099 Table 5.3.1P, EP0099 Table 5.3.2P

In the SS, 15 patients (26.8%) reported any concomitant non AED medications. The 3 most commonly reported concomitant non AED medications, grouped by pharmacological subgroup (level 3), were muscle relaxants, centrally acting agents (4 patients [7.1%]), vitamin A and D, including combinations of the 2 and beta-lactam antibacterials, penicillins (2 patients [3.6%] each).

In the SS, the most frequently selected reasons, from a checklist of reasons, for initiation of brivaracetam were lack of efficacy of current treatment (50 patients [89.3%]) followed by behavioral side effects to current AED (4 patients [7.1%]).

CHMP comment

The largest group of paediatric patients was 13-<18 years old (51.8%). The median age at diagnosis was 4.15 years. Almost all (98%) had seizures at baseline including 89.3% of patients with POS. The median frequency of seizures at 28-day baseline period was 3.33, including POS with frequency 3.33. Majority of patients (64.3%) have been treated with prior ASM with the most often used levetiracetam (46.4%), valproate (16.1%), topiramate (14.3%) and carbamazepine (14.3%). At the time of brivaracetam initiation almost all patients (94.6%) had concomitant ASM medications with the most commonly used medications including valproate, carbamazepine and benzodiazepine.

Number analysed

A total of 56 paediatric patients were enrolled in EP0099.

In the SS, of the 56 paediatric patients who started brivaracetam treatment, 51 patients (91.1%) completed the 12 month study (visits completed) and also had the "Completed" flag selected (Table 7). Three patients (5.4%) who were on brivaracetam treatment discontinued the study prematurely, and the reported reason for premature study termination was lack of efficacy (3 patients [100.0%]). Patients should have had the "Completed" flag selected at the end of the study or should have selected discontinued the study prematurely. Two pediatric patients did not have the "Completed" flag checked and did not indicate they were discontinuing the study prematurely.

A total of 9 patients (16.1%) discontinued brivaracetam treatment prematurely, and the most commonly reported reason for premature brivaracetam discontinuation was lack of efficacy (7 patients [77.8%]). A total of 42 patients (77.8%) who were on brivaracetam treatment were prescribed brivaracetam after exiting the study.

Paediatric patient disposition and discontinuation reasons were similar between the SS and PPS (Table 7).

Table 7: Disposition and discontinuation reasons in paediatric patients (SS and PPS)

Disposition	All paediatric patients (SS) N=56 n (%)	All paediatric patients (PPS) N=28 n (%)
Started BRV	56 (100)	28 (100)
Completed 12-month study: visits completed [a]	51 (91.1)	24 (85.7)
On-BRV when completed [b]	46 (90.2)	22 (91.7)
Not on-BRV when completed [b]	5 (9.8)	2 (8.3)
Completed 12-month study: "completed" flag checked and visits completed [c]	51 (91.1)	24 (85.7)
On-BRV when completed [b]	46 (90.2)	22 (91.7)
Not on-BRV when completed [b]	5 (9.8)	2 (8.3)
Discontinued the study prematurely	3 (5.4)	2 (7.1)
On-BRV when discontinued [b]	3 (100)	2 (100)
Not on-BRV when discontinued [b]	0	0
Primary reason for premature study termination		
Adverse event [b]	0	0
Lack of efficacy [b]	3 (100)	2 (100)
Lost to follow up [b]	0	0
Disease remission [b]	0	0
Consent withdrawn by patient [b]	0	0
Other [b]	0	0

Disposition	All paediatric patients (SS) N=56 n (%)	All paediatric patients (PPS) N=28 n (%)
Discontinued BRV treatment prematurely	9 (16.1)	5 (17.9)
Main reason for BRV discontinuation		
Behavioral side effects [b]	0	0
Other intolerance [b]	1 (11.1)	0
Lack of efficacy [b]	7 (77.8)	4 (80.0)
Other [b]	1 (11.1)	1 (20.0)
Post-study treatment continuation [d]	54 (96.4)	26 (92.9)
Patients being prescribed BRV after exiting the study [b]	42 (77.8)	19 (73.1)
On-BRV when terminated the study [b]	42 (100)	19 (100)
Not on-BRV when terminated the study [b]	0	0
Patients not being prescribed BRV after exiting the study [b]	12 (22.2)	7 (26.9)
On-BRV when terminated the study [b]	7 (58.3)	5 (71.4)
Not on-BRV when terminated the study [b]	5 (41.7)	2 (28.6)

CHMP comment

Out of 56 paediatric patients who entered the study 51 (91%) completed the 12 months study period. This is relatively high proportion of patients considering the usual discontinuation rates in observed in epilepsy studies involving patients with POS. All patients (n=3) who terminated study prematurely did so because of lack of efficacy. Among nine patients who discontinued brivaracetam treatment seven (77.8%) discontinued because of lack of efficacy.

Efficacy results

In the SS, for paediatric patients (total <18 years of age), the brivaracetam retention rate at Month 12 was 83.9%.

In the PPS, for paediatric patients (total <18 years of age), the brivaracetam retention rate at Month 12 was 78.6%, respectively.

Table 8: BRV retention rate at Month 12 by paediatric age group (SS and PPS)

Variable Age group	All paediatric patients (SS) N=56 n/Nsub (%)	All paediatric patients (PPS) N=28 n/Nsub (%)
12-month retention		
Total <18 years	47/56 (83.9)	22/28 (78.6)
4 to <8 years	10/12 (83.3)	4/6 (66.7)
8 to <13 years	11/15 (73.3)	5/8 (62.5)

Variable Age group	All paediatric patients (SS) N=56 n/Nsub (%)	All paediatric patients (PPS) N=28 n/Nsub (%)
13 to <18 years	26/29 (89.7)	13/14 (92.9)

BRV=brivaracetam, eCRF=electronic case report form; PPS=Per-Protocol Set; SS=Safety Set
Note: Nsub is the number of paediatric patients in the SS or PPS for each age group.
Note: n is the number of paediatric patients with 12 months BRV retention (Date of last administration of BRV in Study Termination eCRF or Study Medication Discontinuation eCRF - date of first BRV administration +1 ≥330 days).
Source: EP0099 Table 6.2.3, EP0099 Table 6.2.3.P

In the SS, for paediatric patients (total <18 years of age), brivaracetam retention rates at Month 3 and Month 6 were 100% and 96.4%, respectively.

In the PPS, for paediatric patients (total <18 years of age), brivaracetam retention rates at Month 3 and Month 6 were 100% and 92.9%, respectively.

In the SS, the percentages of paediatric patients (total <18 years of age) achieving seizure freedom from Baseline to Month 3, Month 6, and Month 12 were 35.2%, 22.6%, and 17.0%, respectively.

In the PPS, the percentages of paediatric patients (total <18 years of age) achieving seizure freedom from Baseline to Month 3, Month 6, and Month 12 were 34.6%, 23.1%, and 17.4%, respectively.

Table 9: Seizure freedom from Baseline to Month 3, Month 6, and Month 12 by paediatric age group (SS and PPS)

Age group Visit	All paediatric patients (SS) N=56 n/Nsub (%) 95% CI	All paediatric patients (PPS) N=28 n/Nsub (%) 95% CI
Total <18 years		
Seizure freedom from Baseline to Month 3 visit	19/54 (35.2) (22.7, 49.4)	9/26 (34.6) (17.2, 55.7)
Seizure freedom from Baseline to Month 6 visit	12/53 (22.6) (12.3, 36.2)	6/26 (23.1) (9.0, 43.6)
Seizure freedom from Baseline to Month 12 visit	8/47 (17.0) (7.6, 30.8)	4/23 (17.4) (5.0, 38.8)
4 to <8 years		
Seizure freedom from Baseline to Month 3 visit	4/11 (36.4) (10.9, 69.2)	2/5 (40.0) (5.3, 85.3)
Seizure freedom from Baseline to Month 6 visit	4/12 (33.3) (9.9, 65.1)	2/6 (33.3) (4.3, 77.7)
Seizure freedom from Baseline to Month 12 visit	2/11 (18.2) (2.3, 51.8)	1/5 (20.0) (0.5, 71.6)

Age group Visit	All paediatric patients (SS) N=56 n/Nsub (%) 95% CI	All paediatric patients (PPS) N=28 n/Nsub (%) 95% CI
8 to <13 years		
Seizure freedom from Baseline to Month 3 visit	3/15 (20.0) (4.3, 48.1)	0/8 (0.0, 36.9)
Seizure freedom from Baseline to Month 6 visit	2/13 (15.4) (1.9, 45.4)	0/7 (0.0, 41.0)
Seizure freedom from Baseline to Month 12 visit	2/11 (18.2) (2.3, 51.8)	0/5 (0.0, 52.2)
13 to <18 years		
Seizure freedom from Baseline to Month 3 visit	12/28 (42.9) (24.5, 62.8)	7/13 (53.8) (25.1, 80.8)
Seizure freedom from Baseline to Month 6 visit	6/28 (21.4) (8.3, 41.0)	4/13 (30.8) (9.1, 61.4)
Seizure freedom from Baseline to Month 12 visit	4/25 (16.0) (4.5, 36.1)	3/13 (23.1) (5.0, 53.8)

BRV=brivaracetam; CI=confidence interval; PPS=Per-Protocol Set; SS=Safety Set
Note: Only patients who were still on BRV treatment were included for the analysis.
Note: CIs were calculated using 2-sided Clopper-Pearson exact method.
Note: Percentage was based on the denominator for number of patients in each age group who completed the respective timepoint (Nsub).
Note: n is the number of patients in each age group with seizure freedom from Baseline to the corresponding timepoint. Seizure freedom (Yes) was defined as patients with no seizures recorded prior to the corresponding timepoint (Response to the question: "Has the patient experienced any seizures since the last visit?" was "No" for the corresponding timepoint and all interim visits). If the interim visits were performed and seizure data were missing for the interim visit(s), or if the interim visits were not done, then the patient was defined as not seizure free.
Source: EP0099 Table 6.4.4, EP0099 Table 6.4.4P

In the SS, the percentages of paediatric patients (total <18 years of age) achieving ≥50% POS frequency reduction from Baseline at Month 3, Month 6, and Month 12 were 55.3%, 56.3%, and 87.5%, respectively.

In the PPS, the percentages of paediatric patients (total <18 years of age) achieving ≥50% POS frequency reduction from Baseline at Month 3, Month 6, and Month 12 were 56.5%, 60.9%, and 94.7%, respectively.

Table 10: Paediatric patients, by age group, with response rate (≥50% POS frequency reduction from Baseline) during BRV treatment (SS and PPS)

Age group Visit	All paediatric patients (SS) N=56			All paediatric patients (PPS) N=28		
	n	Yes n (%)	No n (%)	n	Yes n (%)	No n (%)
Total <18 years						
Visit 2 (Month 3)	47	26 (55.3)	21 (44.7)	23	13 (56.5)	10 (43.5)
Visit 3 (Month 6)	48	27 (56.3)	21 (43.8)	23	14 (60.9)	9 (39.1)
Visit 4 (Month 12)	40	35 (87.5)	5 (12.5)	19	18 (94.7)	1 (5.3)
4 to <8 years						
Visit 2 (Month 3)	8	5 (62.5)	3 (37.5)	4	3 (75.0)	1 (25.0)
Visit 3 (Month 6)	10	7 (70.0)	3 (30.0)	5	4 (80.0)	1 (20.0)
Visit 4 (Month 12)	8	7 (87.5)	1 (12.5)	3	3 (100)	0
8 to <13 years						
Visit 2 (Month 3)	13	5 (38.5)	8 (61.5)	8	3 (37.5)	5 (62.5)
Visit 3 (Month 6)	12	6 (50.0)	6 (50.0)	7	2 (28.6)	5 (71.4)
Visit 4 (Month 12)	9	9 (100.0)	0	5	5 (100)	0
13 to <18 years						
Visit 2 (Month 3)	26	16 (61.5)	10 (38.5)	11	7 (63.6)	4 (36.4)
Visit 3 (Month 6)	26	14 (53.8)	12 (46.2)	11	8 (72.7)	3 (27.3)
Visit 4 (Month 12)	23	19 (82.6)	4 (17.4)	11	10 (90.9)	1 (9.1)

BRV=brivaracetam; POS=partial-onset seizure; PPS=Per-Protocol Set; SS=Safety Set
Note: A patient with ≥50% percentage reduction in all types of POS frequency since the last visit (Overall POS Frequency) compared to Baseline seizure frequency was defined as responder = "Yes" or responder = "No" otherwise.
Note: Percentages were based on the number of patients for each age group with non-missing data for percentage reduction from Baseline at each visit.
Source: EP0099 Table 6.6.4P, EP0099 Table 6.6.4.1P

The CGIC was completed at each visit by the treating physician who assessed the paediatric patient's condition over the past 4 weeks compared to Baseline according to 7 categories (1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, and 7=very much worse). The 7 categories of CGIC were also collapsed into 3 categories for analysis purposes: improvement (category 1, 2, or 3), no change (category 4), and worsening (category 5, 6, or 7).

In the SS, the CGIC was completed for 53 pediatric patients (94.6%) at Month 3, 52 patients (92.9%) at Month 6, and 46 patients (82.1%) at Month 12. The majority of patients were assessed to have

improvement in their clinical condition at Month 3 (40 patients [75.5%]) and continued to demonstrate improvement at Month 6 (34 patients [65.4%]) and Month 12 (36 patients [78.3%]). A small percentage of patients were considered by their treating physician to have worsening in their clinical condition at Month 3 (2 patients [3.8%]), Month 6 (6 patients [11.5%]), and Month 12 (3 patients [6.5%]).

The PedsQL at each visit was the paediatric patient's (≥8 to <18 years of age at Baseline) assessment of their HRQoL over the past month through a questionnaire grouped into 4 domains: Physical Functioning, Emotional Functioning, Social Functioning, and School Functioning.

In the SS and PPS, there were limited numbers of paediatric patients who completed the PedsQL questionnaire (range: n=1 to n=8, per visit). In the SS, the mean PedsQL Total score numerically increased from Baseline (62.91) to Month 6 (69.22) in the paediatric patients who completed the questionnaire (ie, contributed to the data).

The Pediatric Cognitive Function Neuro Qol SF at each visit was the paediatric patient's assessment of their perceived difficulties in everyday cognitive abilities, such as memory, attention, concentration, processing speed, and organization skill through an 8 item scale questionnaire.

In the SS and PPS, there were limited numbers of paediatric patients who completed the Pediatric Cognitive Function Neuro QoL SF questionnaire (range: n=1 to n=7 per visit). In the SS, the Pediatric Cognitive Function Neuro QoL SF mean standardized T score numerically increased from Baseline (44.53) to Month 6 (47.08) in the pediatric patients who completed the questionnaire (ie, contributed to the data).

CHMP comments

The retention rate at 12 months for paediatric patients was 83.9% with best retention in the age group of 13<18 years old group (89.7%) and worst one in 8<13 years old group (73.5%). It should be noted that this information was available only for 47 patients despite the fact that 51 patients completed 12 months study period. The seizure freedom at 12 months was achieved by 17% (n=8, out of 47) of patients with similar frequency in all three age groups. It is also noted that 35 out of 40 patients (87.5%) had 50% POS frequency response reduction from baseline at month 12 visit. All 9 patients in the age group 8 to <13 years old had 50% reduction rate.

The PedsQL and Paediatric Cognitive Function Neuro QoL SF questionnaires had very low response rate per visit (from n=1 to n=8 per visit) precluding interpretation of responses.

Safety results

Total brivaracetam exposure

In the SS, the mean (SD) duration of brivaracetam exposure for paediatric patients was 348.3 (65.8) days with the median (Q1, Q3) duration of 368.5 (359.0, 377.5) days. The percentage of paediatric patients with a duration of exposure >12 months (>360 days) was 71.4% (40/56 patients).

Extent of BRV exposure in paediatric patients (SS and PPS)

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
Duration of BRV exposure (days)	n	56	28
	Mean (SD)	348.3 (65.8)	339.9 (82.3)
	Median (Q1, Q3)	368.5 (359.0, 377.5)	370.0 (359.0, 377.5)

Extent of BRV exposure in paediatric patients (SS and PPS)

Variable	Statistic	All paediatric patients (SS) N=56	All paediatric patients (PPS) N=28
	IQR	18.5	18.5
	Min, max	109, 463	109, 463
Duration of BRV exposure	n	56	28
1 day to <3 months (1 to <90 days)	n (%)	0	0
3 months to <6 months (90 to <180 days)	n (%)	2 (3.6)	2 (7.1)
6 months ≤12 months (180 to ≤360 days)	n (%)	14 (25.0)	6 (21.4)
>12 months (>360 days)	n (%)	40 (71.4)	20 (71.4)

BRV=brivaracetam; IQR=interquartile range; max=maximum; min=minimum; PPS=Per-Protocol Set; Q1=25th Percentile; Q3=75th Percentile; SD=standard deviation; SS=Safety Set
Note: Duration of BRV exposure (days)=Date of last administration of BRV while in the study - date of first BRV administration + 1.
Note: Percentages were based on the number of patients in the SS or PPS.
Source: EP0099 Table 7.1.1P, EP0099 Table 7.1.2P

In the SS, the majority of paediatric patients weighing ≥50kg were dosed at ≥50mg/day to ≤100mg/day at Baseline (60.0% [15/25 patients]), and the majority of paediatric patients weighing ≥50kg were dosed at ≥150mg/day to ≤200mg/day at Month 12 (59.1% [13/22 patients]) (EP0099 Table 7.2.1).

In the SS, there was a limited number of paediatric patients weighing ≥10kg to <20kg (n=5). The majority of paediatric patients weighing ≥10kg to <20kg were dosed at ≥1 to ≤2mg/kg/day at Baseline (60.0% [3/5 patients]), and the majority of paediatric patients weighing ≥10kg to <20kg were dosed at >2.5mg/kg/day to ≤4mg/kg/day at Month 12 (75.0% [3/4 patients]) (EP0099 Table 7.2.3).

In the SS, the majority of paediatric patients weighing ≥20kg to <50kg were dosed at ≥1mg/kg/day to ≤2mg/kg/day or >2.5mg/kg/day to ≤4mg/kg/day at Baseline (42.3% [11/26 patients] and 30.8% [8/26 patients], respectively), and the majority of paediatric patients weighing ≥20kg to <50kg were dosed at ≥1mg/kg/day to ≤2mg/kg/day or >2.5mg/kg/day to ≤4mg/kg/day at Month 12 (31.8% [7/22 patients] and 50.0% [11/22 patients], respectively) (EP0099 Table 7.2.3).

Generally, paediatric patients in the SS had higher starting brivaracetam doses and higher brivaracetam doses throughout the study compared with the PPS because patients in the PPS were dosed according to the approved SmPC, current at the time of enrollment in Europe (EP0099 Table 7.2.1, EP0099 Table 7.2.2, EP0099 Table 7.2.3, and EP0099 Table 7.2.4).

In the SS, for paediatric patients weighing ≥50kg, the median (Q1, Q3) total daily dose was 100.000 (100.000, 200.000) mg/day at Baseline and 175.000 (100.000, 200.000) mg/day at Month 12. In the PPS, for paediatric patients weighing ≥50kg, the median total daily dose was 100.000mg/day throughout the study (EP0099 Table 7.3.1 and EP0099 Table 7.3.2).

In the SS, for paediatric patients weighing ≥10kg to <20kg, the median (Q1, Q3) total daily dose was 2.000 (1.923, 2.667) mg/kg/day at Baseline and 2.713 (2.333, 3.379) mg/kg/day at Month 12.

In the SS, for paediatric patients weighing ≥20kg to <50kg, the median (Q1, Q3) total daily dose was 2.029 (1.613, 2.632) mg/kg/day at Baseline and 2.616 (2.000, 3.261) mg/kg/day at Month 12.

CHMP comment

Majority of paediatric patients (71.4%, n=40) were exposed for more than 12 months with median exposure duration of 368.5 days.

It was noted the dose for all three weight categories of paediatric doses increased from baseline to the month 12.

TEAEs

In the SS, 9 patients (16.1%) reported TEAEs; 2 patients (3.6%) reported behavioral TEAEs; 4 patients (7.1%) reported serious TEAEs; 3 patients (5.4%) reported drug related TEAEs; 1 patient (1.8%) reported a TEAE that led to brivaracetam discontinuation. No paediatric patient experienced a fatal AE (table below).

When broken down by time of TEAE occurrence, the majority of patients reported TEAEs occurring within 3 months since the start of treatment with brivaracetam (7 patients [77.8%]).

Table 11: Overview of TEAEs incidence by time of TEAE occurrence in paediatric patients (SS and PPS)

Category	All paediatric patients (SS) N=56 n (%) [#]	All paediatric patients (PPS) N=28 n (%) [#]
Any TEAEs	9 (16.1) [17]	7 (25.0) [15]
<3 months	7 (77.8) [15]	6 (85.7) [14]
3 to <6 months	0	0
6 to <12 months	2 (22.2) [2]	1 (14.3) [1]
≥12 months	0	0
Behavioral TEAEs	2 (3.6) [3]	2 (7.1) [3]
<3 months	2 (100) [3]	2 (100) [3]
3 to <6 months	0	0
6 to <12 months	0	0
≥12 months	0	0
Serious TEAEs	4 (7.1) [6]	3 (10.7) [5]
<3 months	3 (75.0) [5]	3 (100) [5]
3 to <6 months	0	0
6 to <12 months	1 (2.5) [1]	0
≥12 months	0	0
Drug-related TEAEs [a]	3 (5.4) [3]	2 (7.1) [2]
<3 months	1 (33.3) [1]	1 (50.0) [1]

Category	All paediatric patients (SS) N=56 n (%) [#]	All paediatric patients (PPS) N=28 n (%) [#]
3 to <6 months	0	0
6 to <12 months	2 (66.7) [2]	1 (50.0) [1]
≥12 months	0	0
Drug-related serious TEAEs [a]	1 (1.8) [1]	0
<3 months	0	0
3 to <6 months	0	0
6 to <12 months	1 (100) [1]	0
≥12 months	0	0
Patient discontinuations due to TEAEs	1 (1.8) [1]	0
<3 months	0	0
3 to <6 months	0	0
6 to <12 months	1 (100) [1]	0
≥12 months	0	0
Patient discontinuations due to drug-related TEAEs [a]	1 (1.8) [1]	0
<3 months	0	0
3 to <6 months	0	0
6 to <12 months	1 (100) [1]	0
≥12 months	0	0
All deaths (AEs leading to death)	0	0
<3 months	0	0
3 to <6 months	0	0
6 to <12 months	0	0
≥12 months	0	0

Category	All paediatric patients (SS) N=56 n (%) [#]	All paediatric patients (PPS) N=28 n (%) [#]

AE=adverse event; BRV=brivaracetam; PPS=Per-Protocol Set; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: A TEAE was defined as an AE occurring on or after the date of first BRV administration up to 30 days after BRV discontinuation.

Note: n=number of patients reporting at least one TEAE in that category. [#] is the number of individual occurrences of the TEAE in that category. Percentages were based on the number of patients in the analysis set.

Note: The denominator for each time <3 months, 3 to <6 months, 6 to <12 months, and ≥12 months was based on the number of patients in each subcategory. One patient might be counted multiple times.

Note: All Deaths referred to all deaths occurring on study.

Note: Patient discontinuations due to TEAEs were based on TEAEs leading to discontinuation of BRV medication.

Note: Each category of TEAE was continuously stratified by the time of TEAE occurrence (<3 months, 3 to <6 months, 6 to ≤12 months, and ≥12 months since the start of BRV treatment).

[a] Drug-related TEAE was defined per Investigator's assessment. All drug-related TEAEs had a reported relationship.

Source: EP0099 Table 8.1.1P, EP0099 Table 8.1.2P

In the SS, the most frequently reported TEAEs, by SOC, were Nervous system disorders and Psychiatric disorders (3 patients [5.4%], each). The most frequently reported TEAE, by PT, was seizure (2 patients [3.6%]); all other PTs were reported by 1 patient.

In the SS, 2 paediatric patients (3.6%) reported behavioral TEAEs with PTs of laceration (1 patient [1.8%]; 2 events) and aggression (1 patient [1.8%], 1 event). There were no differences between the SS and the PPS.

In the SS, 4 paediatric patients (7.1%) reported serious TEAEs. The serious TEAEs reported by paediatric patients, by PT, were laceration (1 patient [1.8%], 2 events), femur fracture, road traffic accident, epilepsy, and seizure (1 patient [1.8%] each, 1 event each).

Table 12: Incidence of serious TEAEs in paediatric patients (SS and PPS)

MedDRA version 18.1 SOC PT	All paediatric patients (SS) N=56 n (%) [#]	All paediatric patients (PPS) N=28 n (%) [#]
Any serious TEAE	4 (7.1) [6]	3 (10.7) [5]
Injury, poisoning and procedural complications	2 (3.6) [4]	2 (7.1) [4]
Laceration	1 (1.8) [2]	1 (3.6) [2]
Femur fracture	1 (1.8) [1]	1 (3.6) [1]
Road traffic accident	1 (1.8) [1]	1 (3.6) [1]
Nervous system disorders	2 (3.6) [2]	1 (3.6) [1]
Epilepsy	1 (1.8) [1]	1 (3.6) [1]
Seizure	1 (1.8) [1]	-

MedDRA version 18.1 SOC PT	All paediatric patients (SS) N=56 n (%) [#]	All paediatric patients (PPS) N=28 n (%) [#]

MedDRA=Medical Dictionary for Regulatory Activities, PPS=Per-Protocol Set; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event; - =no event reported
Note: n=number of patients reporting at least one serious TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the serious TEAE.
Source: EP0099 Table 8.5.1P, EP0099 Table 8.5.2P

No deaths were reported in paediatric patients.

In the SS, 3 paediatric patients (5.4%) reported drug-related TEAEs. The drug-related TEAEs reported by paediatric patients, by PT, were seizure, hallucination, and insomnia (1 patient [1.8%] each, 1 event each). Of these drug-related TEAEs, the PT of seizure was serious.

In the SS, 1 paediatric patient (1.8%) reported 1 TEAE of seizure that led to brivaracetam discontinuation.

In the SS and PPS, the only other safety relevant information reported by the Investigator in paediatric patients was lack of therapeutic effectiveness of brivaracetam (7 patients [12.5%] and 4 patients [14.3%], respectively).

CHMP comment

Relatively few adverse events were reported by paediatric patients (n=9, 17%). Most of adverse events occurred during first 3 months of treatment. The reported behaviour adverse events (n=2) are already listed in the SmPC. The seizures (n=2) were another most common reported adverse events.

Among serious TEAE two patients reported epilepsy and seizures events each. No deaths were reported in the study.

In summary, no new safety information regarding TEAE were reported.

In the SS, 1 paediatric patient (1.8%) reported a pregnancy during the study. The pregnancy was reported as a nonserious TEAE that was mild in intensity, did not lead to discontinuation, and was reported by the Investigator as not drug-related. The patient was on 100mg/day brivaracetam treatment at the TEAE onset date and continued this dose through the date the TEAE was reported as resolved.

CHMP comment

The one patient who reported a pregnancy continued treatment and reported the event as resolved.

2.3.3. Discussion on clinical aspects

The EP0099 study had the goal to assess long-term utilization and effectiveness and the safety and tolerability of brivaracetam (BRV) adjunctive treatment in patients ≥4 years old with partial-onset seizures (POS) with or without secondary generalization, either added to existing antiepileptic drugs (AED) or replacing another AED therapy in standard medical practice in mid-European countries.

Since this study included paediatric patients the MAH submitted the report summarizing the results in this patients population.

Brivaracetam was prescribed according to routine clinical practice and in accordance with the approved SmPC. No information was provided regarding the specific formulations of brivaracetam used by paediatric patients in this study.

The paediatric patients were only a part of patients' population included into the study. It is noted that only patients > 4years old were included into the study despite the indication allowing treatment of POS in patients from 2 years old.

There were 56 paediatric patients (7%) out of 798 total number recruited patients. Almost all (98%) had seizures at baseline including 89.3% of patients with POS. The median frequency of seizures at 28-day baseline period was 3.33. At the time of brivaracetam initiation almost all patients (94.6%) had concomitant ASM medications with the most commonly used valproate, carbamazepine and benzodiazepine.

Out of 56 paediatric patients who entered the study 51 (91%) completed the 12 months study period. This is relatively high proportion of patients considering the usual discontinuation rates observed in epilepsy studies involving patients with POS. All patients (n=3) who terminated study prematurely did so because of lack of efficacy. Among nine patients who discontinued brivaracetam treatment seven (77.8%) discontinued because of lack of efficacy.

The retention rate at 12 months for paediatric patients was 83.9%. The seizure freedom at 12 months was achieved by 17% (n=8, out of 47) of patients with similar frequency in all three age groups. It is also noted that 35 out of 40 patients (87.5%) had 50% POS frequency response reduction from baseline at month 12 visit.

The PedsQL and Paediatric Cognitive Function Neuro QoL SF questionnaires had very low response rate per visit (from n=1 to n=8 per visit) precluding interpretation of responses.z

Majority of paediatric patients (71.4%, n=40) were exposed for more than 12 months with median exposure duration of 368.5 days. It was noted the dose for all three weight categories of paediatric doses increased from baseline to the month 12.

Relatively few adverse events were reported by paediatric patients (n=9, 17%). Most of adverse events occurred during first 3 months of treatment. The reported behaviour adverse events (n=2) are already listed in the SmPC. The seizures (n=2) were another most common reported adverse events.

Among serious TEAE two patients reported epilepsy and seizures events each. No deaths were reported in the study.

In summary, no new information regarding efficacy of brivaracetam were reported and the safety findings in EP0099 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 EP0099. Safety profile of the paediatric patients who received brivaracetam treatment and completed the study was in line with the established safety profile of brivaracetam. Therefore, the benefit-risk ratio remains unchanged. No changes in the SmPC are considered necessary.

☒ **Fulfilled:**

No regulatory action required.