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Committee for Medicinal Products for Human Use (CHMP)

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

Briviact

Brivaracetam

Procedure no: EMA/PAM/0000295195

Note

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

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

Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	Start of Procedure	15 September 2025	15 September 2025
☐	CHMP Rapporteur AR	20 October 2025	20 October 2025
☐	CHMP Comments	3 November 2025	N/A
☐	Updated CHMP Rapporteur AR	6 November 2025	N/A
☒	CHMP outcome	13 November 2025	13 November 2025

Table of contents

1. Introduction

On 1 September 2025, the MAH submitted a completed paediatric study for Briviact (EP0132), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that "A multicenter, open-label, single-arm study to evaluate long-term safety, tolerability, and efficacy of brivaracetam in study participants 2 to 26 years of age with childhood absence epilepsy or juvenile absence epilepsy" (EP0132) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

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

Brivaracetam (immediate-release film-coated tablet [10, 25, or 50mg] or oral solution [10mg/mL]) was to be administered twice per day in equal doses.

Brivaracetam is approved as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 2 years of age with epilepsy. in the EU.

CHMP comment

The paediatric formulation as well as tablets were used in this study. It is noted that the treated population (childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE)) is outside of the approved indication.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- EP0132 - A multicenter, open-label, single-arm study to evaluate long-term safety, tolerability, and efficacy of brivaracetam in study participants 2 to 26 years of age with childhood absence epilepsy or juvenile absence epilepsy;

2.3.2. Clinical study

EP0132 - A multicenter, open-label, single-arm study to evaluate long-term safety, tolerability, and efficacy of brivaracetam in study participants 2 to

26 years of age with childhood absence epilepsy or juvenile absence epilepsy

Description

EP0132 was a Phase 3, open-label, single-arm, multicenter, long-term follow-up study to evaluate the safety, tolerability, and efficacy of brivaracetam in pediatric study participants with CAE or JAE. The study was designed for study participants in the age range of 2 to 26 years who participated in N01269 and qualified for entry into EP0132.

The EV was the first study visit and was equivalent to the last study visit of the core study as defined in the study protocol of N01269. Two weeks (±2 days) after study start, the study participant was contacted by phone to check on the appropriateness of the brivaracetam dose. Within each year of study participation during the Evaluation Period, Monthly Evaluation Visits (MEVs) were performed at Months 3 and 9, Full Evaluation Visits (FEVs) were performed at Month 6, and Yearly Evaluation Visits (YEVs) were performed at Month 12. At any time, the study participant may have had an Unscheduled Visit if the Investigator or the participant and/or parent(s)/legal representative(s) considered it necessary. For study participants who completed the study, the Evaluation Period lasted from the EV to the FV. For study participants who prematurely discontinued the study, the Evaluation Period lasted from the EV until the EDV.

The duration of the study for each study participant was initially planned to be 2 years at minimum, until approval of brivaracetam for the indication of CAE or JAE was obtained for pediatric participants in their age range, until a managed access program was established as allowed per country specific requirements in addition to legal and regulatory guidelines, or until the investigational product development in the related indication was stopped by the Sponsor, whichever came first. Following the initiation of open-label extension study EP0224 (replacing EP0132) and managed access program EP0225, the duration of EP0132 for many completers was less than 2 years.

Methods

Study participants

All participants enrolled in EP0132 were pediatric participants (<18 years of age). The syndrome category (CAE/JAE) presented in the results is the actual syndrome as reported in N01269.

Treatments

Brivaracetam (immediate-release film-coated tablet [10, 25, or 50mg] or oral solution [10mg/mL]) was to be administered twice per day in equal doses.

Objective(s) Outcomes/endpoints

Table 1: Primary objective

Objectives	Endpoints/estimands
Primary objective	**Primary endpoints**
To investigate the long-term safety and	• TEAEs

Objectives	Endpoints/estimands
tolerability of BRV in pediatric study participants with CAE or JAE	Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the primary safety analysis: 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: TEAE occurrence. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. 4. Population-level summary measure: incidence rates of TEAEs
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• TEAEs leading to discontinuation of study drug Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the primary safety analysis: 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study. 2. Study participant-level outcome: TEAE leading to discontinuation occurrence. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. 4. Population-level summary measure: incidence rates of TEAEs leading to discontinuation.
Primary objective	**Secondary endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• SAEs • Study drug-related TEAEs Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the secondary safety analysis: 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose of BRV during the study.

Objectives	Endpoints/estimands
	2. Study participant-level outcome: occurrence of events in the list above. 3. Intercurrent event handling: The intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all TEAE data are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. 4. Population-level summary measure: incidence rates.
Primary objective	**Other endpoints**
To investigate the long-term safety and tolerability of BRV in pediatric study participants with CAE or JAE	• TEAEs requiring a change in BRV dose • Maximum intensity TEAE experienced (mild, moderate, and severe) • Drug-related serious TEAEs • Fatal AEs • TEAEs by maximum relationship (related and not related to BRV) • SAEs by maximum relationship (related and not related to BRV) Occurrence of other seizure types, including GTCS, based on diary or EEG: • Non-absence seizures based on 1-hour EEG • Non-absence seizures based on diary Estimand: the estimand is defined by the following 4 attributes that will be used to define the treatment effect of interest for the other safety analysis: 1. Population: population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population who receive at least 1 dose BRV during the study. 2. Study participant-level outcome: occurrence of events in the list of endpoints above. 3. Intercurrent event handling: the intercurrent event of concomitant medication use is handled by using a treatment policy strategy in which all AE/TEAE data or seizure data (as applicable) are included, regardless of receipt of any concomitant medication. The intercurrent event of treatment discontinuation is handled by using a while-on-treatment strategy where observation ends at 14 days after treatment is stopped. 4. Population-level summary measure: incidence rates.
To investigate the long-term safety and	• CFB to each applicable visit in safety laboratory tests

Objectives	Endpoints/estimands
tolerability of BRV in pediatric study participants with CAE or JAE	• CFB to each applicable visit in ECG parameters • ECG findings at each applicable visit • Physical and neurological examinations findings at each applicable visit • Psychiatric and mental status at each applicable visit • CFB to each applicable visit in vital signs (blood pressure, pulse rate, body temperature) • CFB to each applicable visit in body weight and height

Table 2: Secondary objective

Objectives	Endpoints/estimands
Secondary objective	**Secondary endpoints**
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom within 4 days prior to or during the 1-hour EEG at each applicable visit up to Month 24 Estimand: 1. Population: the study participant population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population. 2. Study participant-level outcome: seizure freedom response while awake on 1-hour EEG at each applicable visit up to Month 24. 3. Intercurrent event handling: The intercurrent event of concomitant use of any AED, including benzodiazepines, within 4 days prior to or during the 1-hour EEG is handled in the definition of the participant-level variable implementing a composite strategy in which receiving any concomitant AED, including benzodiazepines, within 4 days prior to or during the 1-hour EEG is counted as nonresponse (ie, considered as having absence seizures during the EEG). 4. Population-level summary measure: percentage of study participants free from absence seizures.

To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Absence seizure freedom based on diary over the Evaluation Period truncated at Month 24 and by each applicable 3-month time interval up to Months 22-24 Estimand 5. Population: the study participant population as defined in the protocol-specified inclusion/exclusion criteria reflecting the target patient population. 6. Study participant-level outcome: seizure freedom response on diary over the Evaluation Period truncated at Month 24 and by each applicable 3-month time interval up to Months 22-24. 7. Intercurrent event handling: The intercurrent event of concomitant use of any AED, including benzodiazepines, during each applicable 3-month period is handled in the definition of the participant-level variable implementing a composite strategy in which receiving any concomitant AED, including benzodiazepines, in the 3-month period or during the visit is counted as nonresponse (ie, considered as having absence seizures). The intercurrent event of diary completion during each applicable period is handled in the definition of the participant-level variable implementing a composite strategy in which completing less than 80% of diaries during the 3-month period is counted as nonresponse (ie, considered as having absence seizures). 8. Population-level summary measure: percentage of study participants free from clinical absence seizures.
Secondary objective	**Other endpoints**
To investigate long-term efficacy of BRV in pediatric study participants with CAE or JAE	• Consecutive absence seizure freedom in 6-month periods based on EEG up to Month 24 • Consecutive absence seizure freedom in 6-month periods based on diary up to Month 24

CHMP comments

The primary and secondary objectives of the study are acknowledged and are acceptable.

Sample size

Randomisation and blinding (masking)

Not applicable.

Statistical Methods

For the primary objective, descriptive statistics were provided for AE safety endpoints over the Evaluation Period, for each 3-month period in the Evaluation Period, and for the Overall Period

(Evaluation Period, Down-Titration Period and Safety Period). Clinical laboratory evaluations, vitals signs, and other observations related to safety were summarized by visit. For the secondary objective, descriptive statistics were provided for efficacy endpoints over the Evaluation Period and at regular intervals.

Results

Recruitment

Overall, 84 participants started the study, and there were no screen failures or participants who did not meet eligibility criteria.

The majority of study participants (64 participants [76.2%]) completed the study, 50 participants (59.5%) continued to receive brivaracetam after the study, and 20 participants (23.8%) discontinued the study. The most common primary reasons for premature study discontinuation were consent withdrawn by parent/legal guardian (not due to AE) (7 participants [8.3%]) followed by lack of efficacy (5 participants [6.0%]). There was no notable difference between the study discontinuation rates for participants in the CAE group and JAE group.

Baseline data

In the All participants group, the mean age was 10.60 years (range: 4.0 to 17.0 years), and the majority of study participants were female (48 participants [57.1%]). The majority of study participants were white (77 participants [91.7%]) and not Hispanic or Latino (79 participants [94.0%]). The mean weight, height, and BMI were 42.36kg, 144.06cm, and 19.69kg/m2, respectively.

The mean age, weight, and height were lower in the CAE group than in the JAE group.

Table 3: Demographics (SS)

Variable	CAE N=64	JAE N=20	All participants N=84
Age (years)			
n	64	20	84
Mean (SD)	9.56 (2.49)	13.93 (1.64)	10.60 (2.97)
Median (min, max)	9.50 (4.0, 16.1)	13.83 (11.6, 17.0)	10.33 (4.0, 17.0)
Age [a], n (%)			
24 months to <12 years	53 (82.8)	2 (10.0)	55 (65.5)
12 to <18 years	11 (17.2)	18 (90.0)	29 (34.5)
18 to <65 years	0	0	0

Variable	CAE N=64	JAE N=20	All participants N=84
Age, n (%)			
4 to <6 years	3 (4.7)	0	3 (3.6)
6 to <12 years	50 (78.1)	2 (10.0)	52 (61.9)
12 to <19 years	11 (17.2)	18 (90.0)	29 (34.5)
Gender, n (%)			
Male	27 (42.2)	9 (45.0)	36 (42.9)
Female	37 (57.8)	11 (55.0)	48 (57.1)
Weight (kg)			
n	64	20	84
Mean (SD)	37.92 (15.96)	56.56 (13.13)	42.36 (17.22)
Median (min, max)	34.05 (15.0, 113.4)	53.15 (39.0, 95.0)	40.00 (15.0, 113.4)
Weight (kg)			
<50	50 (78.1)	5 (25.0)	55 (65.5)
≥50	14 (21.9)	15 (75.0)	29 (34.5)
Height (cm)			
n	64	20	84
Mean (SD)	138.93 (15.57)	160.47 (10.39)	144.06 (17.14)
Median (min, max)	143.00 (104.9, 171.5)	161.60 (141.0, 191.0)	146.00 (104.9, 191.0)
BMI at (kg/m^2)			
n	64	20	84
Mean (SD)	19.00 (5.01)	21.89 (4.28)	19.69 (4.98)
Median (min, max)	16.89 (11.8, 38.6)	20.70 (17.4, 36.2)	18.70 (11.8, 38.6)

In the All participants group, the mean absence epilepsy duration from the date of diagnosis to the date of EV in EP0132 was 1.59 years (range: 0.1 to 9.9 years), the mean age at time of absence seizure diagnosis was 8.6 years (range: 0 to 16 years), and the mean percentage of life with absence seizures was 15.2% (range: 0.9% to 98.2%).

The mean absence epilepsy duration was longer, the mean age at time of absence seizure diagnosis was lower, and the mean percentage of life with absence seizures was higher in the CAE group than in the JAE group.

Any medications that were ongoing at the time of entry into EP0132 were to be entered on the EP0132 concomitant medications eCRF. Previous medications included any medications that ended prior to the first dose of study drug in EP0132. Concomitant medications included any medications with at least one day in common with study treatment in EP0132 (including down titration).

No participants reported concomitant medical procedures.

Previous AED medications were used by 5 participants (6.0%) in the All participants group. The most common previous AED, by PT, was valproate (4 participants [4.8%]).

Concomitant AED medications were used by 27 participants (32.1%) in the All participants group. The most common concomitant AEDs, by PT, were ethosuximide and valproate (12 participants [14.3%] each).

There was no notable difference in the overall use of any concomitant AED medications between the CAE group and the JAE group.

The geometric mean (coefficient of variation [%]) plasma concentrations of brivaracetam by modal daily dose category at the Year 1 Months 12 YEV were 0.06725µg/mL (not calculated), 0.1321µg/mL (16,468.3%), 0.4869µg/mL (953.7%), and 1.659µg/mL (49.7%) for brivaracetam >0.0 to <2.0mg/kg/day, ≥2.0 to <3.0mg/kg/day, ≥3.0 to <4.0mg/kg/day, and ≥4.0mg/kg/day, respectively. High interindividual variability in brivaracetam plasma concentrations was caused by participants in which the measured concentrations were BLQ, resulting in an inflated estimate of variability.

Number analysed

The SS consisted of all enrolled study participants who took at least 1 dose of study intervention in EP0132, and all 84 study participants were included in the SS.

Efficacy results

Absence seizure freedom based on 1-hour EEG

Absence seizure freedom within 4 days prior to or during the 1-hour EEG was summarized at each applicable visit up to Month 24. When included, dropouts were imputed as not absence seizure free for all subsequent scheduled visits after the EDV until Month 24.

Absence seizure freedom based on EEG during the Evaluation Period was generally stable at each of the 6-month visits occurring through the Year 2 Month 18 FEV. The proportion of absence seizure free participants in the All participants group ranged from 42.3% to 52.6% (including dropouts) and from 49.1% to 56.4% (excluding dropouts).

Overall, considering the small sample size of the JAE group, particularly at later time points, there were no notable differences in the proportion of absence seizure-free participants in the CAE group and the JAE group.

Absence seizure freedom based on daily seizure diary

Absence seizure freedom based on daily seizure diary was summarized during the Evaluation Period, truncated at Month 24, and by each applicable 3-month time interval up to Months 22-24 for study participants who completed their seizure diary on at least 80% of days within the relevant period.

Absence seizure freedom based on daily seizure diary during the Evaluation Period was generally stable in each 3-month interval from Month 4 to Month 18. The proportion of absence seizure free participants in the All participants group ranged from 40.3% to 43.3% (including dropouts) and from 45.9% to 57.5% (excluding dropouts).

Overall, considering the small sample size of the JAE group, particularly at later time points, there were no notable differences in the proportion of absence seizure-free participants in the CAE group and the JAE group.

Table 4: Overview of results of secondary efficacy endpoints: Absence seizure freedom through Month 18 - including dropouts (SS)

Method Visit/Period	CAE N=64	JAE N=20	All participants N=84
EEG			
Year 1 Month 6 FEV, n1	56	20	76
Absence seizure free, n (%)	26 (46.4)	14 (70.0)	40 (52.6)
Year 1 Month 12 YEV, n1	47	18	65
Absence seizure free, n (%)	20 (42.6)	8 (44.4)	28 (43.1)
Year 2 Month 18 FEV, n1	36	16	52
Absence seizure free, n (%)	14 (38.9)	8 (50.0)	22 (42.3)
Daily seizure diary			
Months 1-3, n1	64	20	84
Absence seizure free, n (%)	22 (34.4)	7 (35.0)	29 (34.5)
Months 4-6, n1	59	20	79
Absence seizure free, n (%)	23 (39.0)	11 (55.0)	34 (43.0)
Months 7-9, n1	53	19	72
Absence seizure free, n (%)	20 (37.7)	11 (57.9)	31 (43.1)
Months 10-12, n1	49	18	67
Absence seizure free, n (%)	19 (38.8)	10 (55.6)	29 (43.3)
Months 13-15, n1	44	18	62
Absence seizure free, n (%)	14 (31.8)	11 (61.1)	25 (40.3)
Months 16-18, n1	39	16	55
Absence seizure free, n (%)	14 (35.9)	9 (56.3)	23 (41.8)

Consecutive absence seizure freedom based on 1-hour EEG

Consecutive absence seizure freedom in 6 month periods was summarized based on EEG up to Month 24. Scheduled and unscheduled EEGs were included in the analyses, and the intercurrent event of concomitant use of any AED, including benzodiazepines, within 4 days prior to or during the 1 hour EEG was not considered in determination of response. Dropouts were imputed as not absence seizure free for all subsequent scheduled visits after the EDV until Month 24.

The proportion of consecutive absence seizure free participants in the All participants group ranged from 64.3% to 65.6% (including dropouts). Up to Month 18, 32 participants (42.7%) (including dropouts) experienced cumulative consecutive absence seizure freedom.

Overall, considering the small sample size of the JAE group, particularly at later time points, there were no notable differences in the proportion of consecutive absence seizure-free or cumulative absence seizure-free participants in the CAE group and the JAE group.

Consecutive absence seizure freedom based on daily seizure diary

Consecutive absence seizure freedom in 6 month periods was assessed based on daily seizure diary up to Month 24. The intercurrent event of concomitant use of any AED, including benzodiazepines, was not considered in determination of response.

The proportions of consecutive absence seizure free participants in the All participants group, including dropouts, were 44.1% during Months 7-12 and 48.2% during Months 13-18. Up to Month 18, 10 participants (14.5%) (including dropouts) experienced cumulative consecutive absence seizure freedom.

Behavior, cognition, and quality of life

Overall, the majority of study participants had an unchanged (36 participants [45.6%]) or improved (34 participants [43.0%]) EpiTrack Junior cognitive performance score at the last assessment compared to Baseline.

CHMP comment

Since this was an open label single arm study the interpretation of results is difficult. However, it could be noted slightly different response in JAE group compared to CAE for absence seizure freedom based on 1-hour EEG recording at 6 months (70% vs 46.4%) and 18 months visits (50% vs 38.9%) (see Table 5-16 above). The similar differences between JAE and CAE were also noted for absence seizure freedom measured by daily seizure diary. Thus, the MAH conclusion that there are no notable differences between JAE and CAE groups, is not supported. The similar changes were also noted for other secondary efficacy endpoints as well as exploratory endpoints (behavior, cognition and quality of life).

However, the value of these observations is difficult to understand and interpret in the absence of control arm and due to small sample size, especially for JAE subgroup.

Safety results

Exposure

In the All participants group, the mean brivaracetam exposure duration during the Evaluation Period was 16.53 months (range: 0.4 to 31.0 months). A total of 57 participants (67.9%) had brivaracetam exposure ≥12 months.

Overall, there were no notable differences in brivaracetam exposure durations between the CAE group and the JAE group.

At exposure durations of ≥12 months, the brivaracetam modal daily dose received by the maximum number of participants (24 participants [42.1%]) was ≥2.0 to <3.0 mg/kg/day.

CHMP comment

Majority of patients had brivaracetam exposure longer than 12 months.

Safety summary

During the Evaluation Period, the incidence of any TEAEs reported was 44.0% in the All participants group (Table 5 1). The most commonly reported TEAE, by PT, was petit mal epilepsy (16.7%). The incidence of TEAEs leading to discontinuation of study intervention and withdrawal from the study was 4.8%, and the most commonly reported TEAE leading to discontinuation of study intervention, by PT, was suicidal ideation (2.4%).

During the Evaluation Period, 3.6% of all participants experienced at least 1 serious TEAE (Table 5 1). The incidence of brivaracetam-related TEAEs (as determined by the Investigator) was 7.1% in the All participants group, and the most commonly reported brivaracetam-related TEAEs, by PT, were headache, somnolence, and suicidal ideation (2.4% each).

Table 5: Summary of TEAEs during the Evaluation Period (SS)

Category	CAE N=64 n (%) [#]	JAE N=20 n (%) [#]	All participants N=84 n (%) [#]
Any TEAEs	26 (40.6) [45]	11 (55.0) [36]	37 (44.0) [81]
Serious TEAEs	2 (3.1) [2]	1 (5.0) [2]	3 (3.6) [4]
TEAEs leading to permanent discontinuation of study intervention	2 (3.1) [2]	2 (10.0) [2]	4 (4.8) [4]
TEAEs requiring dose change	2 (3.1) [3]	4 (20.0) [7]	6 (7.1) [10]
BRV-related TEAEs	4 (6.3) [5]	2 (10.0) [7]	6 (7.1) [12]
Severe TEAEs	2 (3.1) [2]	0	2 (2.4) [2]
All deaths (AEs leading to death)	0	0	0
Deaths (TEAEs leading to death)	0	0	0

AE=adverse event; BRV=brivaracetam; CAE=Childhood Absence Epilepsy; JAE=Juvenile Absence Epilepsy; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: TEAEs were defined as AEs with onset on or after the first dose of BRV in EP0132.
Source: EP0132 CSR Table 7.1.1

During the Evaluation Period, 7.1% of participants experienced TEAEs leading to dose modification. All TEAEs, except 2 of the 4 serious TEAEs, were assessed as mild or moderate by the Investigator. The incidence of brivaracetam related serious TEAEs (as determined by the Investigator) was 1.2% in the All participants group. No fatal AEs were reported in the study. No participants experienced non-absence seizures based on EEG, and 1.2% of participants reported non-absence seizures based on daily seizure diary.

There were no notable trends observed in mean changes from Baseline in clinical laboratory values, vital signs, ECGs, physical examination, neurological examination, and psychiatric and mental status.

CHMP comment

Relatively few patients (44%) reported TEAEs. It is noted that 16.7% of children experienced AE described as petit mal epilepsy. Since this is an old term describing absence epilepsy it is not clear whether those reported AEs could be considered as disease worsening. In addition, the term petit mal epilepsy was in some cases used to describe also focal seizures. Thus, whether these AEs include development of another type of seizures is also not clear.

Most common TEAEs

The incidence of any TEAEs in the All participants group during the Evaluation Period was 44.0% (37 participants) (Table 5 2) and during the Overall Period was 45.2% (38 participants). The most common TEAE, by PT, was petit mal epilepsy (14 participants [16.7%]) during the Evaluation Period and the Overall Period.

Table 6: Incidence of most common TEAEs during the Evaluation Period observed in ≥10% of participants in any group by PT (SS)

MedDRA (v18.1) SOC PT	CAE N=64 n (%) [#]	JAE N=20 n (%) [#]	All participants N=84 n (%) [#]
Any TEAE	26 (40.6) [45]	11 (55.0) [36]	37 (44.0) [81]
General disorders and administration site conditions	4 (6.3) [4]	4 (20.0) [6]	8 (9.5) [10]
Pyrexia	4 (6.3) [4]	4 (20.0) [5]	8 (9.5) [9]
Nervous system disorders	12 (18.8) [15]	8 (40.0) [15]	20 (23.8) [30]
Petit mal epilepsy	9 (14.1) [10]	5 (25.0) [8]	14 (16.7) [18]
Headache	2 (3.1) [3]	2 (10.0) [3]	4 (4.8) [6]
Somnolence	0	2 (10.0) [2]	2 (2.4) [2]

AE=adverse event; BRV=brivaracetam; CAE=Childhood Absence Epilepsy; JAE=Juvenile Absence Epilepsy; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event.
Note: N=number of participants entering each period. n=number of participants reporting at least 1 TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the TEAE.
Note: TEAEs were defined as AEs with onset on or after the first dose of BRV in EP0132.
Source: EP0132 CSR Table 7.2

TEAEs leading to discontinuation of study intervention and Serious TEAEs

The incidence of TEAEs leading to discontinuation of study intervention during the Evaluation Period was 4.8% (4 participants) in the All participants group,. The most common TEAE leading to discontinuation of study intervention, by PT, was suicidal ideation (2 participants [2.4%]).

A total of 3 participants (3.6%) in the All participants group experienced at least 1 serious TEAE during the Evaluation Period, and 4 participants (4.8%) in the All participants group experienced at least 1 serious TEAE during the Overall Period.

During the Evaluation Period, 1 study participant in the CAE group receiving a total dose of brivaracetam 95mg/day experienced a serious TEAE of lymphadenitis that occurred during months 1 to 3 starting on

Day 90 and resolved on Day 93. The event was severe, considered not related to brivaracetam (as determined by the Investigator), and did not lead to study discontinuation.

During the Evaluation Period, 1 study participant in the CAE group receiving a total dose of brivaracetam 120mg/day experienced a serious TEAE of suicidal ideation that occurred during months 7 to 9 starting on Day 269 that was not recovered/resolved. The event was severe, considered related to brivaracetam (as determined by the Investigator), and led to study discontinuation.

During the Evaluation Period, 1 study participant in the JAE group receiving a total dose of brivaracetam 150mg/day experienced a serious TEAE of measles that occurred during months 10 to 12 starting on Day 313 and resolved on Day +2 (2 days after the final dose of brivaracetam) with a duration of 8 days. The event was mild, considered not related to brivaracetam (as determined by the Investigator), and did not lead to study discontinuation. This participant also experienced a serious TEAE of status epilepticus that occurred during months 10 to 12 on Day 318 and resolved the same day. The event was mild, considered not related to brivaracetam (as determined by the Investigator), and led to study discontinuation.

CHMP comment

The suicidal ideations were reported by 2 patients (2.4%). It is noted that the MAH reported that these two cases of suicidal ideation were TEAEs leading to discontinuation of the study. One of them is reported as serious TEAE.

TEAEs by maximum intensity

The majority of TEAEs reported during the Evaluation Period and the Overall Period in the All participants group were mild (22 participants [26.2%] and 23 participants [27.4%], respectively) or moderate (13 participants [15.5%] each) in intensity. During the Evaluation Period and the Overall Period in the All participants group, 2 participants (2.4%) experienced severe TEAEs which included lymphadenitis and suicidal ideation (1 participant [1.2%] each). Both of those severe TEAEs were also serious TEAEs.

Non-absence seizures based on 1-hour EEG or daily seizure diary

No participants experienced non-absence seizures based on EEG during the study.

During the Evaluation Period in the All participants group, 1 study participant (1.2%) from the JAE group reported at least 1 non-absence seizure based on daily seizure diary. This participant experienced a TEAE of generalized tonic-clonic seizure on Day 61. No POS or other type 2 and 3 seizures were reported.

AEs of interest

The incidence of TEAEs of interest during the Evaluation Period and the Overall Period was 23.8% (20 participants) in the All participants group. The most common TEAEs of interest, by PT, were petit mal epilepsy (14 participants [16.7%]) followed by suicidal ideation (2 participants [2.4%]).

One study participant in the CAE group experienced 2 TEAEs of suicidal ideation. The first occurred during months 4 to 6 starting on Day 174 and was not recovered/resolved. The event was nonserious, mild, considered not related to brivaracetam (as determined by the Investigator), and did not lead to study discontinuation. The second event occurred during months 7 to 9 starting on Day 269 and was serious, severe, considered related to brivaracetam (as determined by the Investigator), and led to study discontinuation. One study participant in the JAE group experienced a TEAE of suicidal ideation that occurred during months 10 to 12 starting on Day 344 and resolved on Day 375, was nonserious,

moderate, considered related to brivaracetam (as determined by the Investigator), and led to study discontinuation.

CHMP comment

It is noted that one patient reported two TEAE of suicidal ideation.

Clinical laboratory evaluation

Hematology, Clinical Chemistry, endocrinology and urinalysis

Overall, mean values for hematology, clinical chemistry and endocrinology parameters or urinalysis generally remained within the normal ranges during the study.

Observed changes from Baseline to the Year 1 Month 12 YEV were small in the CAE group and the JAE group. No consistent or clinically relevant brivaracetam related changes from Baseline in mean hematology, clinical chemistry and endocrinology values were observed.

A total of 13 participants (15.5%) had total bilirubin >1.5 x ULN, 8 participants (9.5%), had total bilirubin >2 x ULN, and 4 participants (4.8%) had ALP >1.5 x ULN.

Vital sign measurements, physical examination findings, and other observations related to safety

Observed changes from Baseline to the Year 1 Month 12 YEV were small in the CAE group and the JAE group. No consistent or clinically relevant brivaracetam related changes from Baseline in mean vital signs values were observed.

The overall incidences of any PCST results ranged from 0% to 19.0% in the All participants group among the vital signs parameters evaluated during the study. A total of 14 participants (16.7%) had PCST high values for weight. The majority of these participants were overweight at the EP0132 EV, and no TEAEs related to increased weight were reported.

ECGs

The majority of study participants had normal ECG findings with no abnormalities at Baseline (latest assessment prior to or on the date of first dose in N01269) and remained consistent between Baseline and subsequent visits. A shift from normal to abnormal but not clinically significant ECG findings were reported for 4 participants (4.9%) at the EV, 3 participants (5.5%) at the Year 1 Month 12 YEV, 1 participant (5.6%) at the Year 2 Month 24 YEV, 6 participants (10.7%) at the FV, and 1 participant (33.3%) at the SV. No participants had abnormal clinically significant ECG findings at any visit.

Neurological examination, psychiatric and mental status

The majority of study participants had normal neurological examination findings at Baseline that remained consistent between Baseline and subsequent visits.

The majority of study participants had normal psychiatric and mental findings at Baseline and remained consistent between Baseline and subsequent visits.

During the Evaluation Period, 1 study participant in the CAE group had a positive response on the C SSRS on Day 272 and experienced a serious TEAE of suicidal ideation considered related to brivaracetam (as determined by the Investigator) starting on Day 269 that was not recovered/resolved and led to study discontinuation.

During the Evaluation Period, 1 study participant in the JAE group had psychiatric symptoms reported as Present – Abnormal, clinically significant at the Year 1 Month 12 YEV on Day 371. This participant had psychiatric symptoms not present at Baseline, EV, or Year 1 Month 6 FEV. This participant also had a positive response on the C SSRS on Day 371 and experienced a TEAE of suicidal ideation considered related to brivaracetam (as determined by the Investigator) starting on Day 344 and resolved on Day 375 that led to study discontinuation.

No suicide attempts were reported on the C-SSRS.

CHMP comment

It appears that suicidal ideation is the main issue registered in the study on the C-SSRS.

2.3.3. Discussion on clinical aspects

The MAH submitted a completed paediatric study for Briviact (EP0132), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

This study was a multicenter, open-label, single-arm study to evaluate long-term safety, tolerability, and efficacy of brivaracetam in study participants 2 to 26 years of age with childhood absence epilepsy or juvenile absence epilepsy. The current authorized indication does not cover patients with absence epilepsy which was the targeted population in this study.

The primary objective of the study was to investigate the long-term safety and tolerability of BRV in paediatric study participants with childhood absence epilepsy (CAE) or juvenile absence epilepsy (JAE). The secondary objective of the study was to investigate long-term efficacy of BRV in paediatric study participants with CAE or JAE.

Overall, 84 participants started the study. The majority of study participants (64 participants [76.2%]) completed the study, 50 participants (59.5%) continued to receive brivaracetam after the study, and 20 participants (23.8%) discontinued the study. In the All participants group, the mean age was 10.60 years (range: 4.0 to 17.0 years), and the majority of study participants were female (48 participants [57.1%]). Only 3 patients were younger than 6 years old, all with the CAE. The majority of patients had CAE (n=64).

Since this was an open label single arm study the interpretation of results is difficult. The proportion of absence seizure free participants in the “All participants” group ranged from 42.3% to 52.6%. However, it could be noted slightly different response in JAE group compared to CAE for absence seizure freedom based on 1-hour EEG recording at 6 months (70% vs 46.4%) and 18 months visits (50% vs 38.9%). The similar differences between JAE and CAE were also noted for absence seizure freedom measured as daily seizure diary. Thus, the MAH conclusion that there are no notable differences between JAE and CAE groups, is not supported. The similar changes were also noted for other secondary efficacy endpoints as well as exploratory endpoints (behaviour, cognition and quality of life).

However, the value of these observations is difficult to understand and interpret in the absence of control arm and due to small sample size, especially for JAE subgroup.

Brivaracetam was generally well-tolerated during long term exposure up to 31 months (mean duration 16.53 months) in paediatric study participants in the age range of 4 to 17 years with CAE or JAE. A total of 57 participants (67.9%) had brivaracetam exposure ≥12 months.

44% of patients reported TEAEs. It is noted that 16.7% of children experienced AE described as “petit mal epilepsy”. Since this is an old term describing absence epilepsy it is not clear whether those reported AEs could be considered as disease worsening. In addition, the term “petit mal epilepsy” was in some cases used to describe focal seizures. Thus, whether these AEs include development of another type of seizures is also not clear.

The suicidal ideation was reported by 2 patients (2.4%). It is noted that the MAH reported that these two cases of suicidal ideation were TEAEs leading to discontinuation of the study. One of them is reported as serious TEAE. Suicidal ideation is listed as uncommon ADR in the ADR Table in the SmPC of brivaracetam. However, it is not specifically mentioned among ADRs known for paediatric population.

The safety findings in EP0132 were generally consistent with the known safety profile of brivaracetam. No new safety concerns were identified.

In summary, no new information regarding efficacy of brivaracetam in the approved indication has been reported. The efficacy results in the absence epilepsy are difficult to interpret because of open label nature of the study and absence of the control arm. The safety findings in EP0132 were generally consistent with the known safety profile of brivaracetam.

3. Rapporteur’s overall conclusion and recommendation

No new information regarding efficacy of brivaracetam in the approved indication has been reported. The efficacy results in the absence epilepsy reported in the EP0132 study are difficult to interpret because of open label nature of the study and absence of the control arm. 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.

4. Request for supplementary information

None