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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: EMEA/H/C/003898/P46/010

Note

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

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1. Introduction

On July 4th 2022, the MAH submitted a completed paediatric study for brivarecetam, 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 Open-Label, Single-Arm, Multicenter, Long-Term Study to Evaluate Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Pediatric Subjects with Epilepsy (N01266) is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Brivaracetam (tablet and oral solution) was administered bid approximately 12 hours apart in 2 equally divided doses. Study participants were dosed with either oral tablets or oral solution and not a combination of both. The mg dosage for the oral tablet treatment was calculated to match as closely as possible the mg/kg-based dosage and was a combination of the BRV 10mg, 25mg, and 50mg tablets. Only the following exact dosages were allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day.

The dose of oral solution was measured using the appropriate syringes (1mL, 3mL, and/or 10mL) with an adaptor able to fit both bottle sizes. Oral solution should not have been mixed with other liquids prior to administration.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- N01266 - Open-Label, Single-Arm, Multicenter, Long-Term Study to Evaluate Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Pediatric Subjects with Epilepsy

N01266 - Open-Label, Single-Arm, Multicenter, Long-Term Study to Evaluate Safety and Efficacy of Brivaracetam Used as Adjunctive Treatment in Pediatric Subjects with Epilepsy

Description

N01266 was a Phase 3, open-label, single-arm, multicenter, LTFU study to evaluate the safety and efficacy of BRV in study participants with epilepsy.

Upon enrollment, eligible LTFU study participants entered the Evaluation Period and continued their BRV treatment in accordance with their individualized dose at the completion of the core study. Directly enrolled (DE) study participants were screened and participated in up to 3 weeks of an Up Titration Period. If a DE study participant demonstrated, in the opinion of the Investigator, acceptable

tolerability and seizure control on the same daily dose of BRV (no lower than the minimum specified dose) for 7±2 days during the Up-Titration Period, the study participant attended the Entry Visit (EV) and entered the Evaluation Period on that dose.

For LTFU study participants, the EV was the first study visit. For DE study participants, the EV was the visit at which study participants entered the Evaluation Period and occurred after study participants completed the Screening Visit (ScrV) and at least 1 Titration Visit (TV). For study participants who continued in the study until it ended, the Evaluation Period extended from the EV to the Final Visit (FV). For study participants who prematurely discontinued the study, the Evaluation Period lasted from the EV until the Early Discontinuation Visit (EDV). Following the EDV or following the FV for study participants who completed the study but did not continue BRV treatment, study participants had their BRV dose reduced by a maximum of half the dose every week for a maximum of 4 weeks until a dose of 1mg/kg/day (50mg/day for study participants with body weights >50kg) was reached (Down-Titration Period). After 2 weeks free of IMP (Safety Period), study participants completed the Safety Visit (SV).

Methods

Study participants

Overall, it was planned that approximately 600 study participants would be enrolled in N01266 from a core study; however, study participants from study N01269 were not rolled over to N01266, and studies N01265 and N01268 were not conducted. Therefore, the anticipated number of LTFU study participants for N01266 was approximately 270.

Study participants who enrolled in N01266 from a core study (ie, LTFU study participants from other BRV studies N01263, EP0065, or N01349) must have been ≥1 month to <16 years of age upon entry in the core study; eligible study participants who had POS and enrolled in N01266 without having participated in a core study (ie, directly enrolled [DE] study participants) must have been ≥4 years to <17 years of age.

Below are some key Inclusion criteria for DE study participants only:

8. Study participant was a male or female ≥4 years to <17 years of age.

9. Study participant had a clinical diagnosis of POS according to the International League Against Epilepsy (ILAE) classification.

10. Study participant had an EEG compatible with the clinical diagnosis of POS.

11. Study participant had been observed to have uncontrolled POS after an adequate course of treatment (in the opinion of the Investigator) with at least 1 AED (concurrently or sequentially).

12. Study participant had at least 1 seizure (POS) during the 3 weeks before the ScrV.

13. Study participant was taking at least 1 AED. All AEDs needed to be at a stable dose for at least 7 days before the ScrV. Vagal nerve stimulator stable for at least 2 weeks before the ScrV was allowed and was counted as a concomitant AED. Benzodiazepines taken more than once a week (for any indication) were considered as a concomitant AED.

CHMP comments

In general, the study population included in this study was similar to the one defined in the authorized indication with the exception of some patients from LTFU part (from EP0065 and N01349), which were younger.

Treatments

Immediate-release BRV oral solution and immediate-release, film-coated BRV oral tablets were provided during the study.

Brivaracetam oral solution, at a concentration of 10mg/mL, was supplied in 300mL glass bottles.

Brivaracetam oral tablets were provided in the following strengths: 10mg, 25mg, and 50mg.

There was no placebo or reference product.

Brivaracetam (tablet and oral solution) was administered bid approximately 12 hours apart in 2 equally divided doses. Study participants were dosed with either oral tablets or oral solution and not a combination of both. The mg dosage for the oral tablet treatment was calculated to match as closely as possible the mg/kg-based dosage and was a combination of the BRV 10mg, 25mg, and 50mg tablets. Only the following exact dosages were allowed for the oral tablet administration: BRV 20, 40, 50, 70, 100, 150, and 200mg/day.

For all study participants enrolled in N01266, the maximum BRV dose was 5.0mg/kg/day (2.5mg/kg bid), not to exceed a dose of 200mg/day. Dose adjustments of BRV and/or concomitant antiepileptic drugs [AEDs] were allowed at any time based on clinical judgment; however, during the Up Titration Period, dose adjustments for BRV should have been made only as specified in the protocol.

Objective(s)

The primary objective of N01266 was to document the long-term safety and tolerability of BRV.

The secondary objective of N01266 was to assess the efficacy of BRV during long term exposure.

The following other objectives were studied in N01266:

- To explore direct cost parameters

· To assess the effect of BRV on behavior using the Achenbach Child Behavior Checklist (CBCL) in study participants ≥18 months of age

· To explore the effect of BRV on cognition using the Behavior Rating Inventory of Executive Function® Preschool Version/Behavior Rating Inventory of Executive Function® (BRIEF® P/BRIEF®) in study participants ≥2 years of age

- To assess the effect of BRV on cognition using the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®) in study participants <18 months of age (applicable only to long-term follow-up [LTFU] study participants enrolled in English-speaking countries and countries where a validated translation was available)

· To explore the effect of BRV on health-related quality of life using the Pediatric Quality of Life Inventory™ (PedsQL™) in study participants ≥2 years of age

CHMP comments

The study objectives primarily focused on long-term safety of treatment and are acceptable.

Outcomes/endpoints

Safety

The primary safety variables were as follows:

Treatment-emergent adverse events (TEAEs)

Treatment-emergent serious adverse events (SAEs)

The other safety variables were as follows:

Physical examinations (including Tanner staging, if applicable depending on study participant's developmental status)

Neurological examinations

Psychiatric and mental status

Laboratory tests (hematology, biochemistry, including hepatic monitoring of alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], total bilirubin, and gamma-glutamyltransferase [GGT], endocrinology [follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, triiodothyronine, and tetraiodothyronine] for all study participants and urinalysis for study participants for whom sample collection was feasible) (see N01266 CSR Section 4.1.3.2.1)

Electrocardiogram (ECG)

Vital signs (blood pressure, pulse rate, and body temperature)

Body weight

Height and head circumference

Efficacy

The secondary efficacy variables were as follows:

For study participants ≥2 years of age (based on daily record card [DRC] data):

- Absolute change in 28-days adjusted POS frequency from Baseline to the end of the Evaluation Period (study participants with POS only)
- Percent change in 28-days adjusted POS frequency from Baseline to the end of the Evaluation Period (study participants with POS only)
- 50% responder rate for total seizures (all types)

For study participants <2 years of age (based on electroencephalogram [EEG] data [recorded at least 24 hours]) or study participants with typical absence seizures (based on EEG data):

- Absolute change in average daily frequency (ADF) of POS (study participants with POS only)
- Percent change in ADF of POS (study participants with POS only)
- 50% responder rate for total seizures (all types)

The other efficacy variables were as follows:

For study participants ≥2 years of age (based on DRC data):

- Responder rate (the percentage of study participants who had a ≥50% reduction in seizure frequency per 28 days from Baseline for POS)

- Absolute change in seizure frequency (total seizures) per 28 days from Baseline to the end of the Evaluation Period
- Percent change in seizure frequency (total seizures) per 28 days from Baseline to the end of the Evaluation Period
- Seizure freedom over the Evaluation Period
- Proportion of seizure-free days over the Evaluation Period

For study participants <2 years of age or study participants with typical absence seizures based on the DRC seizure counts:

- Seizure freedom rate over the Evaluation Period (all types) by visit and by time intervals (6 months, 12 months, etc.)
- Proportion of seizure-free days over the Evaluation Period (all types) and by time intervals (6 months, 12 months, etc.)
- Absolute worsening in ADF of total seizures (all types)
- Percent worsening in ADF of total seizures (all types)
- A descriptive summary of seizure frequency by visit based on the DRC data

In addition, for study participants <2 years of age (based on EEG data [recorded at least 24 hours]) or study participants with typical absence seizures (based on EEG data):

- Responder rate for total POS defined as the percentage of study participants with a ≥50% reduction in ADF of POS recorded on EEG
- Absolute change in ADF of total seizures (all types)
- Percent change in ADF of total seizures (all types)
- Seizure freedom (rate and proportion)
- Absolute worsening of other types of seizures
- Percent worsening of other types of seizures
- For study participants with typical absence seizures:
- Number and type of non-absence seizure

Other variables

The other variables for N01266 included the following:

Change from Baseline in the Achenbach CBCL score: the Achenbach CBCL/1½-5 for children from 1½ to 5 years old at the Baseline assessment and the Achenbach CBCL/6-18 for children 6 years and older (age at initiation of investigational medicinal product [IMP] in N01266 or the core study)

Change from Baseline in the BRIEF-P/BRIEF score for study participants ≥2 years of age (age at initiation of IMP in N01266 or the core study)

Change from the Baseline in the Bayley-III scales for children <18 months of age at Baseline of the core study (applicable only to LTFU study participants enrolled in English-speaking countries and in countries where a validated translation was available)

Change from Baseline in PedsQL for study participants ≥2 years of age (age at initiation of IMP in N01266 or core study)

Direct cost parameters: concomitant medications, medical procedures, health care provider consultations not foreseen by the protocol, and hospital stays.

CHMP comments

Efficacy endpoints are provided only as descriptive information. Efficacy variables were analyzed separately for patients < 2 years old and ≥2 years old.

Sample size

Not applicable

Randomisation and blinding (masking)

Not applicable

Statistical Methods

Descriptive statistics are displayed to provide an overview of the study results. For categorical parameters, the number and percentage of study participants in each category are presented. The denominator for percentages is based on the number of study participants appropriate for the purpose of analysis.

Results

Participant flow

Recruitment

Overall, 264 study participants enrolled in the study and 257 study participants (97.3%) were included in the SS, including 127 study participants in the DE cohort and 137 study participants in the LTFU cohort. Seven DE study participants (5.5%) were screen failures.

The number of study participants varied across age groups: 36 study participants in the ≥1 month to <2 years age group, 15 study participants in the ≥2 to <4 years age group, 141 study participants in the ≥4 to <12 years age group, and 65 study participants in the ≥12 to <17 years age group. Due to the low number of participants in the ≥1 month to <2 years and ≥2 to <4 years age groups, any comparison of data across age groups should be made with caution (Table 5 1).

A total of 124 study participants (48.2%) completed the study (Table 5 1), 65 participants (47.4%) in the LTFU cohort and 59 participants (49.2%) in the DE cohort (N01266 CSR Table 1.2.2). Eighteen participants (50.0%) in the ≥1 month to <2 years age group, 4 participants (26.7%) in the ≥2 to <4 years age group, 65 participants (46.1%) in the ≥4 to <12 years age group, and 37 participants (56.9%) in the ≥12 to <17 years age group completed the study (Table 5 1).

Baseline data

Demographics and other Baseline characteristics

Study participant demographics

Study participant demographics are provided overall and by age group for the SS in Table 5–2

Table 5-2: Study participant demographics by age group (SS)

Variable	Descriptive statistic	≥1 month to <2 years N=36	≥2 to <4 years N=15	≥4 to <12 years N=141	≥12 to <17 years N=65	All study participants N=257
Age (years)	n	36	15	141	65	257
	Mean (SD)	1.122 (0.504)	2.761 (0.582)	7.699 (2.394)	13.824 (1.274)	8.039 (4.529)
	Median	1.040	2.830	7.580	13.500	8.170
	Min, max	0.25, 1.92	2.00, 3.83	4.00, 11.92	12.00, 16.92	0.25, 16.92
Gender						
Male	n (%)	17 (47.2)	10 (66.7)	79 (56.0)	35 (53.8)	141 (54.9)
Female	n (%)	19 (52.8)	5 (33.3)	62 (44.0)	30 (46.2)	116 (45.1)
Racial group						
White	n (%)	28 (77.8)	14 (93.3)	107 (75.9)	48 (73.8)	197 (76.7)
Black	n (%)	0	0	2 (1.4)	2 (3.1)	4 (1.6)
Other	n (%)	8 (22.2)	1 (6.7)	32 (22.7)	15 (23.1)	56 (21.8)
Ethnicity						
Hispanic or Latino	n (%)	11 (31.4)	1 (6.7)	38 (27.0)	19 (29.2)	69 (27.0)
Not Hispanic or Latino	n (%)	24 (68.6)	14 (93.3)	103 (73.0)	46 (70.8)	187 (73.0)
Missing	n	1	0	0	0	1
Region						
North America	n (%)	5 (13.9)	4 (26.7)	26 (18.4)	20 (30.8)	55 (21.4)
Latin America	n (%)	10 (27.8)	0	34 (24.1)	17 (26.2)	61 (23.7)
Western Europe	n (%)	5 (13.9)	4 (26.7)	21 (14.9)	13 (20.0)	43 (16.7)
Eastern Europe	n (%)	16 (44.4)	7 (46.7)	60 (42.6)	15 (23.1)	98 (38.1)
Weight (kg)	n	36	15	141	65	257
	Mean (SD)	8.41 (2.85)	12.77 (2.57)	27.22 (11.11)	53.68 (21.05)	30.44 (20.23)
	Median	8.55	12.50	25.00	50.60	26.50
	Min, max	2.6, 15.2	8.5, 17.9	9.1, 84.2	26.2, 156.5	2.6, 156.5
Height (cm)	n	36	15	141	65	257

Table 5-2: Study participant demographics by age group (SS)

Variable	Descriptive statistic	≥1 month to <2 years N=36	≥2 to <4 years N=15	≥4 to <12 years N=141	≥12 to <17 years N=65	All study participants N=257
	Mean (SD)	71.04 (10.69)	89.28 (8.74)	124.43 (16.30)	157.50 (10.48)	123.26 (30.69)
	Median	72.00	87.00	124.00	157.50	126.00
	Min, max	45.0, 90.0	75.5, 110.0	86.0, 160.0	133.0, 181.0	45.0, 181.0
BMI (kg/m^2)	N	36	15	141	65	257
	Mean (SD)	16.148 (2.581)	16.038 (2.530)	16.943 (3.719)	21.254 (6.424)	17.869 (4.810)
	Median	15.974	15.679	16.352	19.228	16.742
	Min, max	10.88, 23.15	12.96, 20.53	9.07, 35.88	12.02, 49.95	9.07, 49.95
BMI category (kg/m^2)						
<18.5	n (%)	28 (77.8)	12 (80.0)	108 (76.6)	25 (38.5)	173 (67.3)
18.5 to <25	n (%)	8 (22.2)	3 (20.0)	29 (20.6)	31 (47.7)	71 (27.6)
25 to <30	n (%)	0	0	3 (2.1)	5 (7.7)	8 (3.1)
≥30	n (%)	0	0	1 (0.7)	4 (6.2)	5 (1.9)
Head circumference (cm)						
	N	35	14	133	61	243
	Mean (SD)	42.33 (4.34)	46.5 (3.57)	51.10 (3.17)	53.89 (3.38)	50.27 (5.02)
	Median	43.20	47.00	51.50	54.00	51.00
	Min, max	31.0, 48.0	40.0, 51.0	42.0, 58.0	43.0, 62.0	31.0, 62.0

BMI=body mass index; DE=directly enrolled; LTFU=long-term follow-up; max=maximum; Min=minimum; ScrV=Screening Visit; SD=standard deviation; SS=Safety Set

Note: Percentages were based on the number of study participants, with available data in each category, in the SS.

Note: Baseline assessments were obtained from the Baseline of previous core studies for LTFU study participants and from the N01266 ScrV for DE study participants.

Data source: N01266 CSR Table 3.1

The histories of epileptic seizures for POS and PGS study participants are presented by age group in Table 5-3 and Table 5-4, respectively.

Table 5-3: History of epileptic seizures for POS study participants (SS)

Statistic	≥1 month to <2 years N=18	≥2 to <4 years N=4	≥4 to <12 years N=112	≥12 to <17 years N=51	All study participants N=185
History of status epilepticus prior to the 1-month period before ScrV, n (%)	1 (5.6)	0	6 (5.4)	0	7 (3.8)
Epilepsy duration (years) [a], n	18	4	112	51	185
Mean (SD)	0.687 (0.510)	1.959 (0.897)	4.612 (2.861)	8.196 (4.155)	5.161 (3.819)
Median	0.704	2.168	4.037	8.824	4.167
Min, max	0.03, 1.84	0.73, 2.77	0.02, 11.31	0.75, 14.90	0.02, 14.90
Age at diagnosis (years), n	18	4	112	51	185
Mean (SD)	0.4689 (0.4758)	0.5777 (0.5943)	3.1619 (2.6294)	5.8108 (3.8170)	3.5743 (3.2840)
Median	0.5270	0.5161	2.8652	5.2567	2.8802
Min, max	0.003, 1.774	0.033, 1.246	0.003, 11.094	0.003, 12.934	0.003, 12.934
Percent of life with epilepsy [a, n]	18	4	112	51	185
Mean (SD)	59.181 (34.451)	74.691 (28.770)	59.025 (29.950)	57.924 (28.160)	59.075 (29.756)
Median	54.908	81.405	62.085	64.239	61.782
Min, max	1.52, 100.00	37.03, 98.92	0.33, 100.00	5.63, 100.00	0.33, 100.00

DE=directly enrolled; eCRF=electronic Case Report Form; LTFU=long-term follow-up; max=maximum; Min=minimum; POS=partial-onset seizure; ScrV=Screening Visit; SD=standard deviation; SS=Safety Set

Note: The POS participants were those who had been categorized as POS participants at Baseline according to N01266 CSR Section 6.1.14.2.

Note: Seizures experienced at any time prior to study entry were summarized.

Note: The history of epilepsy used eCRF information collected at the time of entry into the core studies for LTFU study participants or at the time of entry into N01266 for DE study participants.

[a] Relative to date of first diagnosis.

Data source: N01266 CSR Table 5.3.1

Table 5-4: History of epileptic seizures for PGS study participants (SS)

Statistic	≥1 month to <2 years N=14	≥2 to <4 years N=11	≥4 to <12 years N=29	≥12 to <17 years N=14	All study participants N=68
History of status epilepticus prior to the 1-month period before ScrV, n (%)	0	1 (9.1)	2 (6.9)	0	3 (4.4)
Epilepsy duration (years) [a], n	14	11	29	14	68
Mean (SD)	0.555 (0.403)	2.033 (0.823)	4.719 (2.371)	6.878 (4.487)	3.872 (3.383)
Median	0.519	2.198	4.433	8.593	2.879
Min, max	0.04, 1.18	0.06, 3.48	0.15, 9.82	0.07, 12.47	0.04, 12.47
Age at diagnosis (years), n	14	11	29	14	68
Mean (SD)	0.5978 (0.4769)	0.7907 (0.8897)	2.8089 (2.5074)	6.4150 (4.8017)	2.7697 (3.4160)
Median	0.5051	0.4408	2.0671	4.8350	1.3073
Min, max	0.014, 1.577	0.003, 3.061	0.088, 9.396	0.318, 14.568	0.003, 14.568
Percent of life with epilepsy [a, n]	14	11	29	14	68
Mean (SD)	51.741 (27.803)	74.351 (27.682)	64.557 (27.565)	52.536 (34.875)	61.028 (29.758)
Median	52.179	83.727	71.518	65.747	68.328
Min, max	8.16, 96.12	2.02, 100.00	1.91, 98.21	0.49, 97.54	0.49, 100.00

DE=directly enrolled; eCRF=electronic Case Report Form; LTFU=long-term follow-up; max=maximum; Min=minimum; PGS=primary generalized seizure; ScrV=Screening Visit; SD=standard deviation; SS=Safety Set

Note: The PGS participants were those who had been categorized as PGS participants at Baseline according to N01266 CSR Section 6.1.14.2.

Note: Seizures experienced at any time prior to study entry were summarized.

Note: The history of epilepsy used eCRF information collected at the time of entry into the core studies for LTFU study participants or at the time of entry into N01266 for DE study participants.

[a] Relative to date of first diagnosis.

Data source: N01266 CSR Table 5.3.2

Based on the electronic Case Report Form (eCRF) information collected at the time of entry into the core studies for LTFU participants or at the time of entry into N01266 for DE participants, the majority of study participants overall had POS (185 study participants [72.0%]) and 68 study participants (26.5%) had generalized seizures at the ScrV or 3 weeks prior to the ScrV.

The mean age at time of diagnosis was 0.4689 years in the ≥1 month to <2 years age group, 0.5777 years on the ≥2 to <4 years age group, 3.1619 years in the ≥4 to <12 years age group, and 5.8108 years in the ≥12 to <17 years age group. A total of 7 POS study participants (3.8%) had a history of status epilepticus.

The mean age at time of diagnosis was 0.5978 years in the ≥1 month to <2 years age group, 0.7907 years in the ≥2 to <4 years age group, 2.8089 years in the ≥4 to <12 years age group, and

6.4150 years in the ≥12 to <17 years age group. A total of 3 PGS study participants (4.4%) had a history of status epilepticus.

Table 5-5: Epileptic seizure profile (SS)

	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
At least 1 POS during 3 weeks prior to ScrV	31 (86.1)	15 (100)	140 (99.3)	65 (100)	251 (97.7)
Partial-onset seizures (I)	21 (58.3)	10 (66.7)	121 (85.8)	56 (86.2)	208 (80.9)
Simple partial (IA)	5 (13.9)	4 (26.7)	53 (37.6)	18 (27.7)	80 (31.1)
Complex partial (IB)	11 (30.6)	8 (53.3)	83 (58.9)	42 (64.6)	144 (56.0)
Partial evolving to secondary generalized (IC)	11 (30.6)	6 (40.0)	68 (48.2)	27 (41.5)	112 (43.6)
Primary generalized seizures (II)	13 (36.1)	9 (60.0)	29 (20.6)	15 (23.1)	66 (25.7)
Absence (IIA1)	0	0	4 (2.8)	7 (10.8)	11 (4.3)
Atypical absence (IIA2)	0	1 (6.7)	10 (7.1)	6 (9.2)	17 (6.6)
Myoclonic (IIB)	9 (25.0)	5 (33.3)	9 (6.4)	7 (10.8)	30 (11.7)
Clonic (IIC)	1 (2.8)	3 (20.0)	0	1 (1.5)	5 (1.9)
Tonic (IID)	7 (19.4)	4 (26.7)	9 (6.4)	3 (4.6)	23 (8.9)
Tonic-clonic (IIE)	3 (8.3)	2 (13.3)	12 (8.5)	4 (6.2)	21 (8.2)
Atonic (IIF)	0	2 (13.3)	10 (7.1)	1 (1.5)	13 (5.1)
Unclassifiable (III)	5 (13.9)	2 (13.3)	4 (2.8)	1 (1.5)	12 (4.7)

DE=directly enrolled; eCRF=electronic Case Report Form; LTFU=long-term follow-up; POS=partial-onset seizure; ScrV=Screening Visit; SS=Safety Set
Note: Seizures experienced at any time prior to study entry were summarized.
Note: The history of epilepsy used eCRF information collected at the time of entry into the core studies for LTFU study participants or at the time of entry into N01266 for DE study participants.
Note: The percentages may add to more than 100% as study participant may have been represented in more than 1 category.
Data source: N01266 CSR Table 5.1

The most frequently reported seizures at Baseline were classified as complex partial (144 study participants [56.0%]), followed by partial evolving to secondary generalized (112 study participants [43.6%]). A total of 66 study participants (25.7%) had generalized seizures; the most frequently reported seizures at Baseline were myoclonic (30 study participants [11.7%]), followed by tonic (23 study participants [8.9%]). A total of 12 study participants (4.7%) had a seizure profile classified as unclassifiable (Table 5 5).

A greater proportion of study participants in the ≥2 to <4 years (66.7%), ≥4 to <12 years (85.8%), and ≥12 to <17 years (86.2%) of age groups had a POS profile at Baseline compared with study participants in the ≥1 month to <2 years of age group (58.3%); this would be expected given the study was designed to enroll more study participants with POS in the ≥4 years age groups (DE study participants must have been ≥4 years to <17 years of age [Section 1.3.3]). A greater proportion of study participants in the ≥1 month to <2 years (36.1%) and ≥2 to <4 years (60.0%) age groups had a

primary generalized seizure profile at Baseline compared with study participants in the ≥4 to <12 years (20.6%) and ≥12 to <17 years (23.1%) age groups.

Table 5-6: Baseline classification of epileptic syndromes (SS)

Classification	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
Localization-related	12 (33.3)	4 (26.7)	109 (77.3)	48 (73.8)	173 (67.3)
Idiopathic	1 (2.8)	0	4 (2.8)	1 (1.5)	6 (2.3)
Cryptogenic or symptomatic	11 (30.6)	4 (26.7)	105 (74.5)	47 (72.3)	167 (65.0)
Generalized	15 (41.7)	11 (73.3)	23 (16.3)	16 (24.6)	65 (25.3)
Idiopathic	2 (5.6)	2 (13.3)	7 (5.0)	8 (12.3)	19 (7.4)
Cryptographic or symptomatic	7 (19.4)	5 (33.3)	8 (5.7)	8 (12.3)	28 (10.9)
Symptomatic	6 (16.7)	5 (33.3)	9 (6.4)	1 (1.5)	21 (8.2)
Nonspecific etiology	2 (5.6)	2 (13.3)	5 (3.5)	1 (1.5)	10 (3.9)
Specific syndromes	2 (5.6)	2 (13.3)	3 (2.1)	0	7 (2.7)
Undetermined	5 (13.9)	4 (26.7)	9 (6.4)	4 (6.2)	22 (8.6)
Generalized and focal features	1 (2.8)	2 (13.3)	6 (4.3)	1 (1.5)	10 (3.9)
Other	4 (11.1)	2 (13.3)	3 (2.1)	3 (4.6)	12 (4.7)
Special syndromes	0	1 (6.7)	2 (1.4)	0	3 (1.2)
Situation-related seizures	0	1 (6.7)	2 (1.4)	0	3 (1.2)

DE=directly enrolled; eCRF=electronic Case Report Form; LTFU=long-term follow-up; SS=Safety Set
Note: Seizures experienced at any time prior to study entry were summarized.
Note: The history of epilepsy used eCRF information collected at the time of entry into the core studies for LTFU study participants or at the time of entry into N01266 for DE study participants.
Note: The percentages may add to more than 100% as study participant may have been represented in more than 1 category.
Data source: N01266 CSR Table 5.2.1

A greater proportion of POS study participants had localization-related epileptic syndromes (163/185 study participants [88.1%]) at Baseline compared with PGS study participants and study participants with primary generalized seizure excluding typical absence (PGS*; 10/68 study participants [14.7%] and 10/66 study participants [15.2%], respectively). Whereas a greater proportion of PGS and PGS* study participants had generalized epileptic syndromes (54/68 study participants [79.4%] and 52/66 study participants [78.8%], respectively) at Baseline compared with POS study participants (9/185 study participants [4.9%]).

CHMP comments

The largest group of patients included into the study was 4-12 years old. The majority of patients were coming from Europe with the largest group coming from East Europe (38%).

Most common were complex partial seizures (56%) and the most common type of PGS seizures were myoclonic seizures (30%).

A summary of prior AEDs used by at least 10% of all study participants is presented in Table 7-8.

Table 7-8: Summary of prior AEDs used by ≥10% of all study participants (SS)

WHODD Preferred drug name	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
At least 1 prior AED	27 (75.0)	9 (60.0)	114 (80.9)	52 (80.0)	202 (78.6)
Levetiracetam	6 (16.7)	7 (46.7)	72 (51.1)	29 (44.6)	114 (44.4)
Valproate	6 (16.7)	7 (46.7)	57 (40.4)	28 (43.1)	98 (38.1)
Topiramate	2 (5.6)	5 (33.3)	37 (26.2)	15 (23.1)	59 (23.0)
Carbamazepine	5 (13.9)	0	39 (27.7)	11 (16.9)	55 (21.4)
Oxcarbazepine	1 (2.8)	3 (20.0)	28 (19.9)	16 (24.6)	48 (18.7)
Clobazam	1 (2.8)	1 (6.7)	30 (21.3)	11 (16.9)	43 (16.7)
Lamotrigine	1 (2.8)	1 (6.7)	31 (22.0)	9 (13.8)	42 (16.3)
Clonazepam	1 (2.8)	4 (26.7)	19 (13.5)	10 (15.4)	34 (13.2)
Vigabatrin	9 (25.0)	3 (20.0)	16 (11.3)	6 (9.2)	34 (13.2)
Phenobarbital	6 (16.7)	3 (20.0)	17 (12.1)	7 (10.8)	33 (12.8)

Overall, 252 study participants (98.1%) reported taking at least 1 AED medication at entry into the core study for LTFU study participants and at entry into N01266 for DE study participants. The majority of study participants reported taking 3 or fewer AEDs at study entry: 68 participants (26.5%) reported taking 1 AED, 107 participants (41.6%) reported taking 2 AEDs, and 58 participants (22.6%) reported taking 3 AEDs at study entry. The most commonly reported AEDs taken at study entry were valproate (117 study participants [45.5%]), topiramate (55 study participants [21.4%]), and clobazam (48 study participants [18.7%]).

The concomitant AEDs used by ≥10% of all study participants are summarized in Table 7–10.

Table 7–10: Summary of concomitant AEDs used by ≥10% of all study participants (SS)

WHODD Preferred drug name	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
At least 1 concomitant AED	35 (97.2)	15 (100)	140 (99.3)	65 (100)	255 (99.2)
Valproate	18 (50.0)	7 (46.7)	70 (49.6)	34 (52.3)	129 (50.2)
Clobazam	8 (22.2)	5 (33.3)	40 (28.4)	19 (29.2)	72 (28.0)
Diazepam	8 (22.2)	4 (26.7)	39 (27.7)	17 (26.2)	68 (26.5)
Topiramate	13 (36.1)	2 (13.3)	35 (24.8)	12 (18.5)	62 (24.1)
Lamotrigine	2 (5.6)	3 (20.0)	37 (26.2)	19 (29.2)	61 (23.7)
Phenytoin	3 (8.3)	5 (33.3)	33 (23.4)	15 (23.1)	56 (21.8)
Carbamazepine	4 (11.1)	1 (6.7)	34 (24.1)	14 (21.5)	53 (20.6)
Oxcarbazepine	5 (13.9)	1 (6.7)	30 (21.3)	14 (21.5)	50 (19.5)
Lacosamide	1 (2.8)	2 (13.3)	21 (14.9)	14 (21.5)	38 (14.8)
Clonazepam	4 (11.1)	0	18 (12.8)	7 (10.8)	29 (11.3)
Phenobarbital	11 (30.6)	2 (13.3)	12 (8.5)	1 (1.5)	26 (10.1)
Vigabatrin	10 (27.8)	5 (33.3)	10 (7.1)	1 (1.5)	26 (10.1)

CHMP comments

It is noted that rather large proportion of patients had prior use of levetiracetam reported (44%) as well as valproate (38%).

The most common concomitant ASD was valproate (50%), especially in the youngest patients (≥1 month to < 2 years) - increase from 16.7% to 50%. It is also noted that percentage of patients using at least 1 ASD as a concomitant treatment was similar (99.2%) to the proportion of patients using at least one ASD at the study entry (98.1%) which was higher compared to prior use of ASD (78.6%). Having in mind that study entry for LTFU study participants was defined as the time of entry into the previous core study and for direct enrolled (DE) study participants it was time of entry into N01266, the increased use of concomitant ASD medications complicates interpretation of efficacy results.

Number analysed

Overall, 257 study participants (97.3%) of the 264 study participants enrolled received at least 1 dose of BRV and were included in the SS; 7 DE study participants (5.5%) were screen failures. In addition, 257 study participants (97.3%) had a Baseline and at least 1 completed post-Baseline DRC or EEG and were included in the FAS.

Efficacy results

Secondary efficacy variables for study participants ≥2 years of age (based on DRC data)

Absolute and percent change in 28-day adjusted POS frequency

The absolute and percent change in 28-day adjusted POS frequency from Baseline to the end of the Evaluation Period for study participants ≥2 years of age with POS are summarized for the Full Analysis Set (FAS) in Table 4-1.

Table 4-1: Absolute and percent change in 28-day adjusted POS seizure frequency during the Evaluation Period assessed by DRC (participants ≥2 years of age with POS only) (FAS)

Time period	28-Day ASF Baseline mean	Absolute change			Percent change		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
Months 1 to 3	62.37	134	-41.48 (628.32)	3.90 (-7075.3, 779.3)	105	16.80 (130.50)	51.65 (-759.3, 100.0)
Months 10 to 12	45.01	104	27.08 (82.33)	7.31 (-51.3, 779.0)	80	49.11 (84.35)	64.72 (-576.9, 100.0)
Months 22 to 24	45.15	96	34.14 (90.72)	11.62 (-35.0, 779.3)	73	65.17 (51.13)	87.27 (-129.4, 100.0)
Overall Evaluation Period	62.37	134	-37.48 (628.34)	7.09 (-7075.3, 721.9)	105	26.57 (123.06)	62.92 (-693.7, 100.0)

ADF=average daily frequency; ASF=adjusted seizure frequency; DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation

Note: Baseline mean only used Baseline measurements of participants who contributed data for the respective visit.

Note: Because percent change cannot be calculated for participants with 0 Baseline ADF, n's for absolute change and percent change may differ and do not necessarily capture the same participants.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: Change is defined as decrease in 28-day adjusted POS frequency compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Data source: N01266 CSR Table 7.6.2

Overall, study participants ≥2 years of age with POS reported a median (minimum, maximum) absolute change in POS frequency from Baseline over the Evaluation Period of 7.09 (7075.3, 721.9) per 28 day period and a median (minimum, maximum) percent change in POS frequency of 62.92% (-693.7%, 100.0%) per 28-day period. The large median absolute and percent change values during Months 1 to 3 are due, in part, to a small number of study participants such as Study Participant who had seizure frequencies of 1020.0 at Baseline, 356.0 at Up-Titration, and 8095.3 over the Evaluation Period, resulting in the absolute and percent changes from Baseline of 7075.3 and 693.7%, respectively. The study participant received BRV treatment for 106 days before discontinuing the study due to lack of efficacy.

50% responder rate for total seizures

A summary of the responder rate for all study participants ≥2 years of age during the Evaluation Period based on DRC data is presented for the FAS in Table 4 2. Note that study participants who had no

seizures at Baseline and post-Baseline were regarded as 'not evaluable' for the responder assessment because these participants already had the minimum possible number of seizures.

Table 4-2: Summary of responder rate during the Evaluation Period by seizure category assessed by DRC (all participants ≥2 years of age) (FAS)

	POS N=156 N_{sub}=134 n (%)	PGS N=48 N_{sub}=33 n (%)	All participants N=204 N_{sub}=167 n (%)
Responders	61 (48.4)	20 (60.6)	81 (50.9)
Nonresponders	65 (51.6)	13 (39.4)	78 (49.1)
Not evaluable	8	0	8

DRC=daily record card; FAS=Full Analysis Set; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan
Note: Participants with 0 seizures at Baseline and post Baseline were counted as not evaluable. Percentages for responders and nonresponders are based on evaluable participants only.
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: A responder is defined as a participant with a ≥50% reduction in 28-day adjusted seizure frequency compared with Baseline.
Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.
Note: N_{sub} refers to participants with appropriate Baseline and post-Baseline DRC data for analysis of responder rate.
Note: Because no participants were categorized in the Typical Absence seizure category, PGS* results (PGS excluding typical absence) are not presented as they were equal to PGS results.
Data source: N01266 CSR Table 7.7.1

Overall, 81 study participants (50.9% of all evaluable participants ≥2 years of age) were responders during the Evaluation Period (defined as participants with a ≥50% reduction in the number of seizure days, standardized to a 28 day duration, based on the DRC data). This included 61 study participants with POS (48.4% of evaluable participants ≥2 years of age with POS) and 20 study participants with primary generalized seizures (PGS) (60.6% of evaluable participants ≥2 years of age with PGS).

CHMP comments

In patients ≥2 years of age the absolute numbers and percentage of POS were reduced compared to baseline. In patients with PGS there were more responders (60.6%) compared to patients with POS (48.4%).

Secondary efficacy variables for study participants <2 years of age (based on EEG data)

Absolute and percent change in ADF of POS

The absolute and percent change in POS ADF from Baseline to the end of the Evaluation Period (to the extent of data collected) for study participants <2 years of age with POS are summarized for the FAS in Table 4 3.

Table 4-3: Absolute and percent change in POS ADF during the Evaluation Period assessed by EEG (participants <2 years of age with POS only) (FAS)

Time period	ADF Baseline mean	Absolute change			Percent change		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
MEV Month 3	3.00	7	2.86 (4.49)	0.00 (0.0, 12.0)	3	97.44 (4.44)	100.00 (92.3, 100.0)
FEV Month 6	2.29	7	2.29 (4.86)	0.00 (0.0, 13.0)	2	100.00 (0.00)	100.00 (100.0, 100.0)
Overall Evaluation Period	2.63	8	2.56 (4.44)	0.00 (0.0, 12.5)	3	98.72 (2.22)	100.00 (96.2, 100.0)

ADF=average daily frequency; EEG=electroencephalogram; FAS=Full Analysis Set; FEV=Full Evaluation Visit; max=maximum; MEV=Minimal Evaluation Visit; min=minimum; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation

Note: Baseline mean only used Baseline measurements of participants who contributed data for the respective visit.

Note: Because percent change cannot be calculated for participants with 0 Baseline ADF, n's for absolute change and percent change may differ and do not necessarily capture the same participants.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: Change was defined as decrease in POS ADF compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Data source: N01266 CSR Table 7.1.2.1

Overall, study participants <2 years of age with POS reported a median (minimum, maximum) absolute change in POS ADF from Baseline to the end of Evaluation Period of 0.00 (0.0, 12.5) and a median (minimum, maximum) percent change in POS ADF of 100.00% (96.2%, 100.0%). The positive mean and median absolute changes from Baseline at Months 3 and 6 (based on EEG) support that the ADF of POS counts in participants <2 years of age was maintained (if study participants had 0 seizures at Baseline) or improved (if study participants had ≥1 seizure at Baseline) over the course of N01266

50% responder rate for total seizures

A summary of the responder rate for all study participants <2 years of age during the Evaluation Period (to the extent of data collected) based on EEG data is presented for the FAS in Table 4-4.

Table 4-4: Summary of responder rate during the Evaluation Period by seizure category assessed by EEG (all LTFU participants <2 years of age) (FAS)

	POS N=40 N_{sub}=8 n (%)	PGS N=46 N_{sub}=6 n (%)	All participants N=86[a] N_{sub}=14 n (%)
Responders	4 (100)	2 (50.0)	6 (75.0)
Nonresponders	0	2 (50.0)	2 (25.0)
Not evaluable	4	2	6

ADF=average daily frequency; EEG=electroencephalogram; FAS=Full Analysis Set; LTFU=long-term follow-up; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan

Note: Participants with 0 seizures at Baseline and post Baseline are counted as not evaluable. Percentages for responders and nonresponders are based on evaluable participants only.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: A responder is defined as a participant with a ≥50% reduction in ADF compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Note: N_{sub} refers to participants with appropriate Baseline and post-Baseline EEG data for analysis of responder rate.

Note: Because no participants were categorized in the Typical Absence seizure category, PGS* results (PGS excluding typical absence) are not presented as they were equal to PGS results.

[a] N=86 represents the total number of LTFU study participants who were not excluded from the efficacy analysis (EP0065, N01349).

Data source: N01266 CSR Table 7.2.1.1

CHMP comments

Numbers of study participants <2 years of age were very limited and observed results is difficult to interpret. This age group is currently not covered by the approved indication.

Other efficacy variables for study participants ≥2 years of age (based on DRC data)

Responder rate for POS

A summary of the responder rate (the percentage of study participants who had a ≥50% reduction in seizure frequency per 28 days from Baseline) for POS for all study participants ≥2 years of age during the Evaluation Period based on DRC data is presented for the FAS in Table 4-5.

Table 4-5: Summary of POS responder rate during the Evaluation Period by seizure category assessed by DRC (all participants ≥2 years of age) (FAS)

	POS N=156 N_{sub}=134 n (%)	PGS N=48 N_{sub}=33 n (%)	All participants N=204 N_{sub}=167 n (%)
Responders	60 (47.6)	5 (26.3)	65 (44.8)
Nonresponders	66 (52.4)	14 (73.7)	80 (55.2)
Not evaluable	8	14	22

DRC=daily record card; FAS=Full Analysis Set; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan

Note: Participants with 0 seizures at Baseline and post Baseline are counted as not evaluable. Percentages for responders and nonresponders are based on evaluable participants only.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: A responder is defined as a participant with a ≥50% reduction in 28-day adjusted POS seizure frequency compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Note: N_{sub} refers to participants with appropriate Baseline and post-Baseline DRC data for analysis of POS responder rate.

Note: Because no participants were categorized in the Typical Absence seizure category, PGS* results (PGS excluding typical absence) are not presented as they were equal to PGS results.

Data source: N01266 CSR Table 7.7.2

Absolute and percent change in seizure frequency

The absolute and percent change in 28-days adjusted total seizure frequency from Baseline to the end of the Evaluation Period for all study participants ≥2 years of age are summarized for the FAS in Table 4-6.

Table 4-6: Absolute and percent change in 28-day adjusted total seizure frequency during the Evaluation Period assessed by DRC (participants ≥2 years of age) (FAS)

Time period	28-Day ASF Baseline mean	Absolute change			Percent change		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
Months 1 to 3	90.27	167	-14.86 (569.15)	7.38 (-7075.3, 779.3)	139	22.93 (118.41)	52.80 (-759.3, 100.0)
Months 10 to 12	61.99	125	33.64 (82.79)	13.42 (-94.0, 778.4)	101	50.90 (76.80)	64.22 (-576.9, 100.0)
Months 22 to 24	61.96	114	41.27 (89.81)	20.69 (-35.0, 777.5)	91	65.21 (47.06)	83.00 (-129.4, 100.0)
Overall Evaluation Period	90.27	167	-12.33 (566.66)	16.86 (-7075.3, 680.0)	139	31.32 (111.84)	60.32 (-693.7, 100.0)

Table 4-6: Absolute and percent change in 28-day adjusted total seizure frequency during the Evaluation Period assessed by DRC (participants ≥2 years of age) (FAS)

Time period	28-Day ASF Baseline mean	Absolute change			Percent change		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)

ADF=average daily frequency; ASF=adjusted seizure frequency; DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; SAP=Statistical Analysis Plan; SD=standard deviation

Note: Baseline mean only used Baseline measurements of participants who contributed data for the respective visit.

Note: Because percent change cannot be calculated for participants with 0 Baseline ADF, n's for absolute change and percent change may differ and do not necessarily capture the same participants.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: Change is defined as decrease in 28-day adjusted seizure frequency compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Data source: N01266 CSR Table 7.6.1

Overall, study participants ≥2 years of age reported a median (minimum, maximum) absolute change in total seizure frequency from Baseline to the end of Evaluation Period of 16.86 (7075.3, 680.0) per 28 day period and a median (minimum, maximum) percent change in total seizure frequency of 60.32% (-693.7%, 100.0%) per 28-day period.

Seizure freedom

A summary of seizure freedom based on DRC data during the Evaluation Period for study participants ≥ 2 years of age with POS is presented for the FAS in Table 4-7.

Table 4-7: Seizure freedom during the Evaluation Period assessed by DRC (participants ≥2 years of age with POS only) (FAS)

Time interval Category	N_{sub}=165 n (%)
Months 1 to 3, N_{sub}	**164**
Seizure free	33 (20.1)
Not seizure free	131 (79.9)
Not collected	0
Months 10 to 12, N_{sub}	**129**
Seizure free	43 (33.3)
Not seizure free	86 (66.7)
Not collected	0
Months 22 to 24, N_{sub}	**118**
Seizure free	46 (39.0)
Not seizure free	72 (61.0)
Not collected	0
Evaluation Period	**165**

Table 4-7: Seizure freedom during the Evaluation Period assessed by DRC (participants ≥2 years of age with POS only) (FAS)

Time interval Category	N_{sub}=165 n (%)
Seizure free	16 (9.8)
Not seizure free	148 (90.2)
Not collected	1

DRC=daily record card; FAS=Full Analysis Set; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: This summary used the definition of seizure freedom in N01266 SAP Section 3.10.3.1.
Note: Percentages use the number of participants entering the Evaluation Period with at least 1 DRC entry as the denominator; see N01266 SAP Section 3.10.3.1.
Note: A participant was defined as seizure-free if they had no occurrence of seizures in the Evaluation Period assessed by DRC.
Note: N_{sub} refers to participants with appropriate Baseline and post-Baseline DRC data for analysis of seizure freedom.
Data source: N01266 CSR Table 7.11.1 and N01266 CSR Table 7.11.2

Proportion of seizure-free days

The proportion of POS seizure-free days based on DRC data during the Evaluation Period for study participants ≥2 years of age with POS is presented for the FAS in Table 4 8.

Table 4.8: Proportion of seizure-free days during the Evaluation Period assessed by DRC (participants ≥2 years of age with POS only) (FAS)

Time period	n	Mean (SD)	Median (min, max)
Overall Evaluation Period	157	0.760 (0.298)	0.904 (0.01, 1.00)

DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: n is the number of participants with at least 1 DRC entry in the respective time period.
Note: The proportion of seizure-free days is calculated as defined in N01266 SAP Section 3.10.3.1.
Data source: N01266 CSR Table 7.10.1

CHMP comments

Other efficacy variables for all study participants ≥2 years of age – absolute and percent change in 28-days adjusted total seizure frequency from Baseline to the end of the Evaluation Period, seizure freedom, proportion of seizure free days during the evaluation period, - are pointing to the same direction as secondary efficacy variables.

Other efficacy variables for study participants <2 years of age (based on DRC data)

Seizure freedom

A summary of seizure freedom based on DRC data during the Evaluation Period for participants <2 years of age with POS, by 3-month time interval, is presented for the FAS in Table 4-9.

Table 4-9: Seizure freedom during the Evaluation Period assessed by DRC (participants <2 years of age with POS only) (FAS)

Time interval Category	N_{sub}=18 n (%)
Months 1 to 3, N_{sub}	**18**
Seizure free	4 (22.2)
Not seizure free	14 (77.8)
Not collected	0
Months 10 to 12, N_{sub}	**15**
Seizure free	8 (53.3)
Not seizure free	7 (46.7)
Not collected	0
Months 22 to 24, N_{sub}	**7**
Seizure free	4 (57.1)
Not seizure free	3 (42.9)
Not collected	0
Evaluation Period	**18**
Seizure free	3 (16.7)
Not seizure free	15 (83.3)
Not collected	0

DRC=daily record card; FAS=Full Analysis Set; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: This summary used the definition of seizure freedom in N01266 SAP Section 3.10.3.1.
Note: Percentages use the number of participants entering the Evaluation Period with at least 1 DRC entry as the denominator; see N01266 SAP Section 3.10.3.1.
Note: A participant was defined as seizure-free if they had no occurrence of seizures in the Evaluation Period assessed by DRC.
Note: N_{sub} refers to participants with appropriate Baseline and post-Baseline DRC data for analysis of seizure freedom.
Data source: N01266 CSR Table 7.11.1 and N01266 CSR Table 7.11.2

Proportion of seizure free days

The proportion of POS seizure-free days based on DRC data during the Evaluation Period for participants <2 years of age with POS is presented for the FAS in Table 4 10.

Table 4-10: Proportion of seizure-free days during the Evaluation Period assessed by DRC (participants <2 years of age with POS only) (FAS)

Time period	n	Mean (SD)	Median (min, max)
Overall Evaluation Period	18	0.782 (0.351)	0.964 (0.03, 1.00)

Table 4-10: Proportion of seizure-free days during the Evaluation Period assessed by DRC (participants <2 years of age with POS only) (FAS)

Time period	n	Mean (SD)	Median (min, max)

DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: N is the number of participants with at least 1 DRC entry in the respective time period.
Note: The proportion of seizure-free days is calculated as defined in N01266 SAP Section 3.10.3.1.
Data source: N01266 CSR Table 7.10.1

Absolute and percent worsening of PGS

The absolute and percent worsening in PGS ADF from Baseline to the end of the Evaluation Period for participants <2 years of age with POS are summarized in Table 4-11.

Table 4-11: Absolute and percent worsening in PGS ADF during the Evaluation Period assessed by DRC (participants <2 years of age with POS only) (FAS)

Time period	28-Day ASF Baseline mean	Absolute worsening			Percent worsening		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
Months 1 to 3	384.58	10	-318.82 (473.21)	-40.62 (-1401.3, 10.8)	10	-80.56 (34.44)	-92.90 (-99.9, 12.8)
Months 10 to 12	422.33	9	-369.34 (511.74)	-73.42 (-1508.9, -37.3)	9	-93.25 (9.35)	-99.86 (-100.0, -77.9)
Months 22 to 24	163.72	6	-160.82 (206.85)	-58.10 (-560.0, -37.3)	6	-96.62 (8.14)	-100.00 (-100.0, -80.0)
Overall Evaluation Period	384.58	10	-308.55 (431.76)	-39.60 (-1248.1, -32.7)	10	-85.79 (19.71)	-96.86 (-100.0, -45.4)

ADF=average daily frequency; ASF=adjusted seizure frequency; DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; PGS=partial generalized seizure; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation
Note: Baseline mean only used Baseline measurements of participants who contributed data for the respective visit.
Note: Because percent worsening cannot be calculated for participants with 0 Baseline ADF, n's for absolute worsening and percent worsening may differ and do not necessarily capture the same participants.
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: Worsening is defined as increase in 28-day adjusted PGS seizure frequency compared with Baseline.
Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.
Data source: N01266 CSR Table 7.8.1

Overall, study participants <2 years of age with POS reported a median (minimum, maximum) absolute worsening in PGS ADF based on DRC from Baseline to the end of Evaluation Period of 39.60 (1248.1, -32.7) and a median (minimum, maximum) percent worsening in PGS ADF of 96.86% (-100.0%, -45.4%) (Table 4-11) (negative data for worsening indicate a reduction of PGS seizure frequency in these analyses).

Seizure frequency by time period

The ADF by time interval for participants <2 years of age with POS is presented for the FAS in Table 4 12.

Table 4-12: ADF during the Evaluation Period by time period assessed by DRC (participants <2 years of age with POS only) (FAS)

Time period	n	Mean (SD)	Median (min, max)
Months 1 to 3	18	1.894 (4.695)	0.050 (0.00, 19.12)
Months 4 to 6	16	1.172 (3.179)	0.006 (0.00, 12.76)
Months 7 to 9	16	2.587 (8.138)	0.000 (0.00, 32.87)
Months 10 to 12	15	1.547 (3.951)	0.000 (0.00, 15.28)
Months 13 to 15	11	3.571 (9.713)	0.000 (0.00, 32.59)
Months 16 to 18	9	3.530 (8.702)	0.000 (0.00, 26.32)
Months 19 to 21	9	4.119 (11.931)	0.000 (0.00, 35.93)
Months 22 to 24	7	0.089 (0.226)	0.000 (0.00, 0.60)
Months 25 to 27	6	0.198 (0.411)	0.028 (0.00, 1.03)
Months 28 to 30	5	0.113 (0.155)	0.044 (0.00, 0.37)
Months 31 to 33	6	0.150 (0.244)	0.017 (0.00, 0.60)
Months 34 to 36	6	0.137 (0.197)	0.022 (0.00, 0.42)
Months 37 to 39	6	0.307 (0.737)	0.006 (0.00, 1.81)
Months 40 to 42	6	0.234 (0.350)	0.100 (0.00, 0.92)
Months 43 to 45	6	0.341 (0.679)	0.033 (0.00, 1.71)
Months 46 to 48	6	0.476 (0.977)	0.006 (0.00, 2.44)
Months 49 to 51	6	0.601 (1.023)	0.033 (0.00, 2.52)
Months 52 to 54	5	0.679 (1.338)	0.141 (0.00, 3.07)
Months 55 to 57	6	0.316 (0.754)	0.006 (0.00, 1.86)
Months 58 to 60	6	0.426 (1.000)	0.011 (0.00, 2.47)
Months 61 to 63	6	0.450 (1.102)	0.000 (0.00, 2.70)
Months 64 to 66	6	0.424 (1.028)	0.006 (0.00, 2.52)
Months 67 to 69	6	0.346 (0.848)	0.000 (0.00, 2.08)
Months 70 to 72	6	0.497 (1.205)	0.006 (0.00, 2.96)
Months 73 to 75	6	0.357 (0.870)	0.000 (0.00, 2.13)
Months 76 to 78	6	0.656 (1.584)	0.000 (0.00, 3.89)
Months 79 to 81	3	0.421 (0.710)	0.022 (0.00, 1.24)
Months 82 to 84	2	0.000 (0.000)	0.000 (0.00, 0.00)
Months 85 to 87	2	0.006 (0.008)	0.006 (0.00, 0.01)

Table 4-12: ADF during the Evaluation Period by time period assessed by DRC (participants <2 years of age with POS only) (FAS)

Time period	n	Mean (SD)	Median (min, max)
Months 88 to 90	2	0.011 (0.016)	0.011 (0.00, 0.02)
Months 91 to 93	2	0.000 (0.000)	0.000 (0.00, 0.00)
Months 94 to 96	2	0.006 (0.008)	0.006 (0.00, 0.01)
Months 97 to 99	2	0.006 (0.008)	0.006 (0.00, 0.01)
Months 100 to 102	2	0.000 (0.000)	0.000 (0.00, 0.00)
Months 103 to 105	2	0.033 (0.047)	0.033 (0.00, 0.07)
Months 106 to 108	1	0.000 (--)	0.000 (0.00, 0.00)
Overall Evaluation Period	18	1.909 (5.776)	0.052 (0.00, 24.59)

ADF=average daily frequency; DRC=daily record card; FAS=Full Analysis Set; max=maximum; min=minimum; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Data source: N01266 CSR Table 7.8.2

During the Evaluation Period, study participants <2 years of age with POS reported a median (minimum, maximum) ADF of 0.052 (0.00, 24.59). In general, median ADF decreased or was maintained from Months 1 to 3 onward compared with Baseline, although there were fewer participants in the later months.

Other efficacy variables for study participants <2 years of age (based on EEG data)

Responder rate for total POS

A summary of the responder rate for total POS (defined as the percentage of study participants with a ≥50% reduction in ADF of POS recorded on EEG) during the Evaluation Period (to the extent of data collected) for all participants <2 years of age is presented for the FAS in Table 4 13.

Table 4-13: Summary of POS responder rate during the Evaluation Period by seizure category assessed by EEG (all participants <2 years of age) (FAS)

	POS N=40 N_{sub}=8 n (%)	PGS N=46 N_{sub}=6 n (%)	All participants N=86 N_{sub}=14 n (%)
Responders	3 (100)	2 (66.7)	5 (83.3)
Nonresponders	0	1 (33.3)	1 (16.7)
Not evaluable	5	3	8

ADF=average daily frequency; EEG=electroencephalogram; FAS=Full Analysis Set; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan
Note: Participants with 0 seizures at Baseline and post Baseline are counted as not evaluable. Percentages for responders and nonresponders are based on evaluable participants only.
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: A responder is defined as a participant with a ≥50% reduction in POS ADF compared with Baseline.
Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.
Note: N_{sub} refers to participants <2 years of age with appropriate Baseline and post-Baseline EEG data for analysis of POS responder rate.
Note: Because no participants were categorized in the Typical Absence seizure category, PGS* results (PGS excluding typical absence) are not presented as they were equal to PGS results.
Data source: N01266 CSR Table 7.2.2.1

Overall, 5 study participants (83.3% of all evaluable participants <2 years of age) were POS responders during the Evaluation Period (defined as participants with a ≥50% reduction in ADF, based on the EEG data). This included 3 participants with POS (100% of evaluable participants with POS <2 years of age) and 2 participants with PGS (66.7% of evaluable participants with PGS <2 years of age).

Absolute and percent change in ADF of total seizures

The absolute and percent change in ADF from Baseline over the Evaluation Period (to the extent of data collected) for participants <2 years of age with POS based on EEG are summarized in Table 4-14.

Table 4-14: Absolute and percent change in ADF during the Evaluation Period assessed by EEG (participants <2 years of age with POS only) (FAS)

Time period	ADF Baseline mean	Absolute change			Percent change		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
MEV Month 3	3.14	7	3.00 (4.40)	1.00 (0.0, 12.0)	4	98.08 (3.85)	100.00 (92.3, 100.0)
FEV Month 6	2.43	7	2.43 (4.79)	0.00 (0.0, 13.0)	3	100.00 (0.00)	100.00 (100.0, 100.0)
Overall Evaluation Period	2.75	8	2.69 (4.37)	0.50 (0.0, 12.5)	4	99.04 (1.92)	100.00 (96.2, 100.0)

ADF=average daily frequency; EEG=electroencephalogram; FAS=Full Analysis Set; FEV=Full Evaluation Visit; max=maximum; MEV=Minimal Evaluation Visit; min=minimum; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation

Note: Baseline mean only used Baseline measurements of participants who contributed data for the respective visit.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: Because percent change cannot be calculated for participants with 0 Baseline ADF, n's for absolute change and percent change may differ and do not necessarily capture the same participants.

Note: Change was defined as decrease in ADF compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Data source: N01266 CSR Table 7.1.1.1

Overall, participants <2 years of age with POS reported a median (minimum, maximum) absolute change in ADF from Baseline to the end of Evaluation Period of 0.50 (0.0, 12.5) and a median (minimum, maximum) percent change in ADF of 100.0% (96.2%, 100.0%).

Seizure freedom (rate and proportion)

A summary of seizure freedom based on EEG data during the Evaluation Period (to the extent of data collected) for participants <2 years of age with POS is presented for the FAS in Table 4-15.

Table 4-15: Seizure freedom during the Evaluation Period assessed by EEG (participants <2 years of age with POS only) (FAS)

Category	N_{sub}=18 n (%)
Seizure free	8 (88.9)
Not seizure free	1 (11.1)
Not collected	9

EEG=electroencephalogram; FAS=Full Analysis Set; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan
Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.
Note: This summary used the definition of seizure freedom in N01266 SAP Section 3.10.3.1.
Note: Percentages use the number of participants entering the Evaluation Period with at least 1 EEG assessment as the denominator; see N01266 SAP Section 3.10.3.1.
Note: A participant was defined as seizure-free if they had no occurrence of seizures in the Evaluation Period assessed by EEG.
Note: N_{sub} refers to participants with appropriate Baseline and post-Baseline EEG data for analysis of seizure freedom.
Data source: N01266 CSR Table 7.3.1

Among 9 study participants <2 years of age with POS in the Evaluation Period with at least 1 EEG assessment, 8 study participants (88.9%) were seizure free (defined as participants with no occurrence of POS in the Evaluation Period, based on the EEG data).

Absolute and percent worsening of PGS

The absolute and percent worsening in PGS ADF from Baseline to the end of the Evaluation Period (to the extent of data collected) for participants <2 years of age with POS based on EEG are summarized for the FAS in Table 4-16.

Table 4-16: Absolute and percent worsening in PGS ADF during the Evaluation Period assessed by EEG (participants <2 years of age with POS only) (FAS)

Time period	ADF Baseline mean	Absolute worsening			Percent worsening		
		n	Mean (SD)	Median (min, max)	n	Mean (SD)	Median (min, max)
MEV Month 3	0.14	7	-0.14 (0.38)	0.00 (-1.0, 0.0)	1	-100.00	-100.00 (-100.0, -100.0)
FEV Month 6	0.14	7	-0.14 (0.38	0.00 (-1.0, 0.0)	1	-100.00	-100.00 (-100.0, -100.0)
Overall Evaluation Period	0.13	8	-0.13 (0.35)	0.00 (-1.0, 0.0)	1	-100.00	-100.00 (-100.0, -100.0)

ADF=average daily frequency; EEG=electroencephalogram; max=maximum; min=minimum; NA=not applicable; PGS=primary generalized seizure; POS=partial-onset seizure(s); SAP=Statistical Analysis Plan; SD=standard deviation

Note: Baseline mean only used Baseline measurements of participants who contributed data for the respective visit.

Note: Because percent worsening cannot be calculated for participants with 0 Baseline ADF, n's for absolute worsening and percent worsening differ.

Note: Seizure category at Baseline according to N01266 SAP Section 3.10.3.

Note: Worsening was defined as increase in PGS ADF compared with Baseline.

Note: EP0065 and N01349 participants did not provide appropriate Baseline data and were excluded in the planned analyses.

Data source: N01266 CSR Table 7.4.1

Overall, study participants <2 years of age with POS reported a median (minimum, maximum) absolute worsening in PGS ADF based on EEG from Baseline to Month 3, Month 6, and the end of Evaluation Period of 0.00 (1.0, 0.0), each (Table 4-16) (negative data for worsening indicate a reduction of PGS seizure frequency in these analyses). Only 1 participant <2 years of age with POS had data to calculate percent worsening in PGS ADF during the Evaluation Period.

CHMP comments

Numbers of study participants <2 years of age were very low thus interpretation of the observed efficacy endpoints is difficult.

Other efficacy variable – Study participants with typical absence seizures

There were 2 study participants with typical absence seizures; neither of these study participants reported non-absence seizures during the course of the study.

Other efficacy variable – Direct cost parameters

For study participants overall who remained in the study and on BRV treatment, higher proportions of study participants achieved fewer health care provider visits and hospital stays over time, with similar observations across age groups.

Safety results

Treatment exposure

A total of 264 study participants had been enrolled and 257 received BRV treatment in N01266 with a mean of 3.2 study-participants years of exposure. Of these, 184 study participants (71.6%) had been exposed to BRV for at least 12 months, 151 study participants (58.8%) had been exposed to BRV for at least 24 months, 113 study participants (44.0%) had been exposed to BRV for at least 36 months, 88 study participants (34.2%) had been exposed to BRV for at least 48 months, and 74 study participants (28.8%) had been exposed to BRV for at least 60 months.

Table 8–2: BRV exposure (SS)

	≥1 month to <2 years N=36	≥2 to <4 years N=15	≥4 to <12 years N=141	≥12 to <17 years N=65	All study participants N=257
Evaluation Period BRV exposure duration (months)					
n	36	15	139	65	255
Mean (SD)	35.92 (37.41)	31.69 (35.57)	42.97 (31.87)	31.31 (22.36)	38.34 (31.12)
Min, max	1.1, 113.5	1.0, 110.3	0.6, 114.3	1.0, 94.2	0.6, 114.3
Overall study BRV exposure duration (months)					
n	36	15	141	65	257
Mean (SD)	36.10 (37.36)	31.94 (35.49)	42.57 (31.91)	31.50 (22.30)	38.24 (31.07)
Min, max	1.3, 113.5	1.0, 110.3	0.2, 114.3	1.2, 94.2	0.2, 114.3
Evaluation Period BRV exposure duration category, n (%)					
Evaluation Period overall	36 (100)	15 (100)	139 (98.6)	65 (100)	255 (99.2)
≤6 months	4 (11.1)	4 (26.7)	26 (18.4)	12 (18.5)	46 (17.9)
>6 to ≤12 months	8 (22.2)	3 (20.0)	9 (6.4)	5 (7.7)	25 (9.7)
>12 to ≤18 months	7 (19.4)	2 (13.3)	4 (2.8)	1 (1.5)	14 (5.4)
>18 to ≤24 months	5 (13.9)	0	10 (7.1)	4 (6.2)	19 (7.4)
>24 to ≤30 months	1 (2.8)	1 (6.7)	13 (9.2)	6 (9.2)	21 (8.2)
>30 to ≤36 months	0	0	4 (2.8)	14 (21.5)	18 (7.0)
>36 months	11 (30.6)	5 (33.3)	73 (51.8)	23 (35.4)	112 (43.6)

Exposure to BRV by modal dose is presented in Table 8-3.

Table 8-3: Modal dose exposure to BRV (SS)

	BRV overall N=257	BRV modal dose (mg/kg/day)				
		>0.0 to 1.0 N=5	>1.0 to 2.0 N=22	>2.0 to 3.0 N=39	>3.0 to 4.0 N=66	>4.0 N=125
Mean participant years of exposure	3.2	1.7	1.9	2.1	2.9	4.0
Number of study participants exposed by duration of exposure, n (%)						
≤6 months	257 (100)	5 (100)	22 (100)	39 (100)	66 (100)	125 (100)
>6 months	209 (81.3)	3 (60.0)	14 (63.6)	30 (76.9)	53 (80.3)	109 (87.2)
>12 months	184 (71.6)	3 (60.0)	9 (40.9)	27 (69.2)	45 (68.2)	100 (80.0)
>18 months	170 (66.1)	3 (60.0)	7 (31.8)	24 (61.5)	40 (60.6)	96 (76.8)
>24 months	151 (58.8)	3 (60.0)	6 (27.3)	17 (43.6)	38 (57.6)	87 (69.6)
>36 months	113 (44.0)	1 (20.0)	4 (18.2)	7 (17.9)	26 (39.4)	75 (60.0)
>48 months	88 (34.2)	0	4 (18.2)	4 (10.3)	21 (31.8)	59 (47.2)
>60 months	74 (28.8)	0	4 (18.2)	3 (7.7)	17 (25.8)	50 (40.0)
>72 months	50 (19.5)	0	3 (13.6)	3 (7.7)	9 (13.6)	35 (28.0)
>84 months	25 (9.7)	0	0	2 (5.1)	4 (6.1)	19 (15.2)
>96 months	7 (2.7)	0	0	0	0	7 (5.6)
>108 months	5 (1.9)	0	0	0	0	5 (4.0)

CHMP comments

The 257 patients received BRV treatment in N01266 with a mean of 3.2 study-participants years of exposure. However, only 6 out of 15 patients in ≥2 to <4 years age group were exposed for more than 18 months. Thus, even after the completion of the study the information regarding long-term exposure in this age group is very limited.

Overall summary of TEAEs

An overview of TEAEs by age group is presented for the SS in Table 5 8.

Table 5-8: Overview of TEAEs by age group (SS)

	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
Any TEAE	34 (94.4)	14 (93.3)	132 (93.6)	60 (92.3)	240 (93.4)
Serious TEAEs	14 (38.9)	8 (53.3)	42 (29.8)	19 (29.2)	83 (32.3)
Discontinuation due to TEAE	4 (11.1)	5 (33.3)	15 (10.6)	7 (10.8)	31 (12.1)
IMP-related TEAEs	7 (19.4)	7 (46.7)	46 (32.6)	19 (29.2)	79 (30.7)
Severe TEAEs	11 (30.6)	6 (40.0)	21 (14.9)	6 (9.2)	44 (17.1)
IMP-related serious TEAEs	1 (2.8)	0	3 (2.1)	1 (1.5)	5 (1.9)
TEAEs leading to death	2 (5.6)	2 (13.3)	2 (1.4)	1 (1.5)	7 (2.7)

AE=adverse event; BRV=brivaracetam; IMP=investigational medicinal product; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: TEAEs were defined as AEs that had onset on or after the day of first BRV dose.
Note: n=number of study participants reporting a TEAE for that specific category of AE.
Note: Percentages were relative to the number of study participants in the SS.
Note: Each study participant was counted at most once for each category.
Data source: N01266 CSR Table 12.1.1

The incidences of TEAEs (range: 88.8% to 97.7%), discontinuations due to TEAEs (range: 10.2% to 14.8%), and severe TEAEs (range: 14.8% to 18.6%) were similar across geographic regions. The incidence of SAEs was higher in Western Europe (46.5%) compared with the other geographic regions (range: 27.9% to 32.7%) and the incidence of IMP related TEAEs was lower in Latin America (19.7%) compared with the other geographic regions (range: 32.7% to 37.2%).

The most common TEAEs (ie, those TEAEs experienced by ≥10% of all study participants) are presented by age group in Table 5 9.

Table 5-9: Most common TEAEs (≥10% of all study participants) by age group (SS)

MedDRA v.18.1 SOC PT	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
At least 1 TEAE	34 (94.4)	14 (93.3)	132 (93.6)	60 (92.3)	240 (93.4)
Gastrointestinal disorders	**22 (61.1)**	**6 (40.0)**	**68 (48.2)**	**21 (32.3)**	**117 (45.5)**
Vomiting	11 (30.6)	5 (33.3)	35 (24.8)	4 (6.2)	55 (21.4)
Diarrhoea	7 (19.4)	0	21 (14.9)	8 (12.3)	36 (14.0)
General disorders and administration site conditions	**16 (44.4)**	**6 (40.0)**	**50 (35.5)**	**17 (26.2)**	**89 (34.6)**
Pyrexia	15 (41.7)	5 (33.3)	38 (27.0)	7 (10.8)	65 (25.3)
Infections and infestations	**28 (77.8)**	**12 (80.0)**	**107 (75.9)**	**40 (61.5)**	**187 (72.8)**
Nasopharyngitis	11 (30.6)	4 (26.7)	44 (31.2)	16 (24.6)	75 (29.2)
Pharyngitis	10 (27.8)	2 (13.3)	39 (27.7)	8 (12.3)	59 (23.0)
Upper respiratory tract infection	10 (27.8)	5 (33.3)	23 (16.3)	8 (12.3)	46 (17.9)
Pharyngotonsillitis	5 (13.9)	0	21 (14.9)	10 (15.4)	36 (14.0)
Gastroenteritis	8 (22.2)	0	18 (12.8)	5 (7.7)	31 (12.1)
Influenza	5 (13.9)	2 (13.3)	16 (11.3)	2 (3.1)	29 (11.3)
Bronchitis	7 (19.4)	3 (20.0)	16 (11.3)	2 (3.1)	28 (10.9)
Metabolism and nutrition disorders	**8 (22.2)**	**3 (20.0)**	**25 (17.7)**	**12 (18.5)**	**48 (18.7)**
Decreased appetite	6 (16.7)	1 (6.7)	16 (11.3)	7 (10.8)	30 (11.7)
Nervous system disorders	**16 (44.4)**	**8 (53.3)**	**74 (52.5)**	**37 (56.9)**	**135 (52.5)**
Seizure	3 (8.3)	3 (20.0)	24 (17.0)	12 (18.5)	42 (16.3)
Headache	0	1 (6.7)	22 (15.6)	16 (24.6)	39 (15.2)
Somnolence	3 (8.3)	1 (6.7)	17 (12.1)	6 (9.2)	27 (10.5)
Respiratory, thoracic, and mediastinal disorders	**14 (38.9)**	**8 (53.3)**	**46 (32.6)**	**14 (21.5)**	**82 (31.9)**
Cough	6 (16.7)	2 (13.3)	19 (13.5)	5 (7.7)	32 (12.5)

AE=adverse event; BRV=brivaracetam; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: Treatment-emergent adverse events were defined as AEs that had onset on or after the day of first BRV dose.
Note: n=number of study participants reporting a TEAE for the specified SOC or PT.
Note: Percentages were relative to the number of study participants in the SS.
Note: Each study participant was counted at most once for each SOC and PT.
Data source: N01266 CSR Table 12.2.1.1

A total of 240 study participants (93.4%) experienced TEAEs, most frequently reported in the system organ class (SOC) of Infections and infestations (187 study participants [72.8%]), followed by Nervous system disorders (135 study participants [52.5%]), and Gastrointestinal disorders (117 study

participants [45.5%]). Overall, the most frequently reported TEAEs (by preferred term [PT]) were nasopharyngitis (75 study participants [29.2%]), pyrexia (65 study participants [25.3%]), and pharyngitis (59 study participants [23.0%]) (Table 5 9).

In considering most common ongoing TEAEs by 3-month time interval, a higher proportion of study participants experiencing TEAEs was observed during the first 3 months of treatment (195 study participants [75.9%]) compared with the subsequent time intervals, with an overall trend of similar TEAEs over time.

In considering most common TEAEs by total duration of exposure cohorts, across total duration of exposure cohorts, the most frequent TEAEs experienced were consistently nasopharyngitis, pyrexia, vomiting, pharyngitis, seizure, and diarrhea. Study participants who remained on BRV for periods longer than 30 months experienced increased incidence of PTs in the SOC of Infections and infestations (eg, upper respiratory tract infection, gastroenteritis, cough, and rhinitis).

Most common TEAEs by study period

A total of 120 DE study participants entered the Up-Titration Period and 59 DE study participants (49.2%) experienced TEAEs, most frequently in the SOCs of Infections and infestations (22 study participants [18.3%]) and Psychiatric disorders (20 study participants [16.7%]). Overall, the incidence of TEAEs (by PT) was low (<6%) with irritability (7 study participants [5.8%]) and decreased appetite, diarrhea, and cough (6 study participants [5.0%] each) being most frequently reported.

One DE study participant (1/120 study participants [0.8%]) experienced a TEAE of suicidal ideation during the Up Titration Period. Nine study participants (9/255 study participants [3.5%]) experienced TEAEs of suicidal ideation during the Evaluation Period (DE n=7, LTFU n=2). One study participant (DE) (1/124 study participants [0.8%]) experienced a TEAE of suicidal ideation during the Safety Period.

A total of 255 study participants entered the Evaluation Period and a majority experienced TEAEs during this period (233 study participants [91.4% of all study participants]). The most frequently reported TEAEs overall were nasopharyngitis (73 study participants [28.6%]) and pyrexia (61 study participants [23.9%]).

Eighty-six study participants entered the Down-Titration Period, and 9 study participants (10.5%) experienced TEAEs. Varicella, nasopharyngitis, and status epilepticus were reported by 2 study participants (2.3%) each; the remaining PTs were reported by 1 participant each.

One hundred twenty-four study participants were evaluated during the Safety Period and 22 study participants (17.7%) experienced TEAEs. Pharyngitis was reported by 3 study participants (2.4%) and pyrexia, nasopharyngitis, and seizure were reported by 2 participants (1.6%) each; the remaining PTs were reported by 1 participant each.

Treatment-emergent AEs by maximum intensity

Overall, a majority of study participants experienced TEAEs with a maximum intensity of mild (60 study participants [23.3%]) or moderate (136 study participants [52.9%]). A total of 44 study participants (17.1%) experienced severe TEAEs. The most frequently reported severe TEAEs were seizure (7 study participants [2.7%]), pneumonia (7 study participants [2.7%]), and status epilepticus (5 study participants [1.9%]); no other severe TEAEs were experienced by more than 2 study participants.

Treatment-emergent AEs considered related to BRV by the Investigator

Treatment-emergent AEs considered related to BRV per Investigator assessment that occurred in ≥2 study participants (by age group) are presented in Table 5-10.

Table 5-10: IMP-related TEAEs occurring in ≥2 study participants by age group (SS)

MedDRA v.18.1 SOC PT	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
At least 1 IMP-related TEAE	**7 (19.4)**	**7 (46.7)**	**46 (32.6)**	**19 (29.2)**	**79 (30.7)**
Gastrointestinal disorders	**0**	**0**	**5 (3.5)**	**0**	**5 (1.9)**
Vomiting	0	0	2 (1.4)	0	2 (0.8)
General disorders and administration site conditions	**1 (2.8)**	**2 (13.3)**	**7 (5.0)**	**3 (4.6)**	**13 (5.1)**
Fatigue	0	2 (13.3)	4 (2.8)	3 (4.6)	9 (3.5)
Asthenia	1 (2.8)	0	2 (1.4)	0	3 (1.2)
Investigations	**3 (8.3)**	**0**	**5 (3.5)**	**1 (1.5)**	**9 (3.5)**
Gamma-glutamyltransferase increased	0	0	2 (1.4)	1 (1.5)	3 (1.2)
Weight decreased	1 (2.8)	0	2 (1.4)	0	3 (1.2)
Metabolism and nutrition disorders	**0**	**1 (6.7)**	**7 (5.0)**	**3 (4.6)**	**11 (4.3)**
Decreased appetite	0	1 (6.7)	7 (5.0)	3 (4.6)	11 (4.3)
Nervous system disorders	**2 (5.6)**	**1 (6.7)**	**18 (12.8)**	**9 (13.8)**	**30 (11.7)**
Somnolence	0	1 (6.7)	8 (5.7)	3 (4.6)	12 (4.7)
Seizure	1 (2.8)	0	2 (1.4)	3 (4.6)	6 (2.3)
Drooling	0	0	2 (1.4)	0	2 (0.8)
Epilepsy	0	0	2 (1.4)	0	2 (0.8)
Tremor	0	0	2 (1.4)	0	2 (0.8)
Psychiatric disorders	**0**	**3 (20.0)**	**24 (17.0)**	**9 (13.8)**	**36 (14.0)**
Aggression	0	2 (13.3)	7 (5.0)	1 (1.5)	10 (3.9)
Insomnia	0	1 (6.7)	4 (2.8)	0	5 (1.9)
Abnormal behaviour	0	0	3 (2.1)	1 (1.5)	4 (1.6)
Irritability	0	0	4 (2.8)	0	4 (1.6)
Confusional state	0	0	1 (0.7)	2 (3.1)	3 (1.2)
Attention deficit/hyperactivity disorder	0	0	2 (1.4)	0	2 (0.8)
Hallucination	0	0	2 (1.4)	0	2 (0.8)

Table 5-10: IMP-related TEAEs occurring in ≥2 study participants by age group (SS)

MedDRA v.18.1	≥1 month to <2 years	≥2 to <4 years	≥4 to <12 years	≥12 to <17 years	All study participants
SOC	N=36	N=15	N=141	N=65	N=257
PT	n (%)	n (%)	n (%)	n (%)	n (%)

AE=adverse event; BRV=brivaracetam; IMP=investigational medicinal product; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: Treatment-emergent adverse events were defined as AEs that had onset on or after the day of first BRV dose.

Note: n=number of study participants reporting a TEAE for the specified category of AE.

Note: Percentages were relative to the number of study participants in the SS.

Note: An AE was considered to be related to IMP if either the relationship to IMP was specified as related by the Investigator or the relationship to IMP was not specified.

Data source: N01266 CSR Table 12.3.1

CHMP comments

The most common TEAEs are similar to the ones described in the SmPC. No new unexpected TEAEs were reported.

Adverse events of special interest

There were no study participants who reported TEAEs of special interest. Three study participants reported 4 TEAEs that were erroneously marked as TEAEs of special interest. These TEAEs did not meet the predefined criteria described in the protocol for being of special interest; however, cases were not resolved by data cleaning before lock of the data base. Therefore, these cases are reported:

- 1 event of seizure (nonserious, mild, did not lead to discontinuation)
- 2 events of simple partial seizures in 1 participant (1 event was nonserious and moderate, 1 event was serious and moderate, and both led to discontinuation)
- 1 event of epididymitis (serious, moderate, did not lead to discontinuation)

Deaths

Seven study participants died during the study. A by participant listing of AEs with an outcome of death is provided in N01266 CSR Listing 9.2.4 and is presented in Table 5-11.

Table 5-11: AEs with an outcome of death (SS)

Study participant number/cohort/gender/age (years)/race/weight (kg)	AE onset/outcome date (Relative days)/Study Period	AE preferred term	Serious/Intensity	Relationship to IMP	Action taken with IMP
/LTFU/M/	363/+1/Evaluation	Acute respiratory failure	Yes/Severe	Not related	Drug withdrawn
		Aspiration	Yes/Severe	Not related	Drug withdrawn
		Circulatory collapse	Yes/Severe	Not related	Drug withdrawn
/LTFU/F/	887/+13/Evaluation	Pneumonia	Yes/Severe	Not related	Drug withdrawn
		Septic shock	Yes/Severe	Not related	Drug withdrawn
/LTFU/F/	146/146/Evaluation	Pneumonia	Yes/Severe	Not related	Drug withdrawn
/DE/M/	188/188/Evaluation	Circulatory collapse	Yes/Severe	Not related	Drug withdrawn
/LTFU/M/	177/177/Evaluation	Pneumonia aspiration	Yes/Severe	Not related	Drug withdrawn
/LTFU/M/	+1/+1/--	Apnoea	Yes/Severe	Not related	Drug withdrawn
/DE/M/	2623/2638/Evaluation	Corona virus infection	Yes/Moderate	Not related	Drug withdrawn

AE=adverse event; DE=directly enrolled; F=female; IMP=investigational medicinal product; LTFU=long-term follow-up; M=male; SS=Safety Set
Data source: N01266 CSR Listing 9.2.4

CHMP comments

Seven patients died during the study according to the Table 5-11 "AEs with an outcome of death (SS)". Patients' age ranged from 0.58 to 14 years old. Two patients were directly enrolled (DE) into the study, while remaining were from the LTFU. The relationship to the IMP was considered as not related by the MAH.

It is noted that another fatal outcome was presented in the Table 5-13 "AEs leading to discontinuation (SS)". Patient (LTFU/F/) died from pneumonia on day 81 from the treatment onset. Addition of this patient to the list would make the most common cause of death pneumonia (n=4). The second most common cause of death was circulatory collapse (n=2). Other death causes were reported in single individual patients.

Other serious adverse events

Serious TEAEs that occurred in ≥2 study participants are presented by age group in Table 5-12.

Table 5-12: Incidence of serious TEAEs occurring in ≥2 study participants by age group (SS)

PT	≥1 month to <2 years N=36 n (%)	≥2 to <4 years N=15 n (%)	≥4 to <12 years N=141 n (%)	≥12 to <17 years N=65 n (%)	All study participants N=257 n (%)
At least 1 serious TEAE	**14 (38.9)**	**8 (53.3)**	**42 (29.8)**	**19 (29.2)**	**83 (32.3)**
Seizure	1 (2.8)	1 (6.7)	12 (8.5)	2 (3.1)	16 (6.2)
Status epilepticus	2 (5.6)	0	7 (5.0)	2 (3.1)	11 (4.3)
Pneumonia	3 (8.3)	0	4 (2.8)	1 (1.5)	8 (3.1)
Pyrexia	2 (5.6)	1 (6.7)	3 (2.1)	0	6 (2.3)
Dehydration	1 (2.8)	0	3 (2.1)	1 (1.5)	5 (1.9)
Generalised tonic-clonic seizure	1 (2.8)	1 (6.7)	2 (1.4)	1 (1.5)	5 (1.9)
Somnolence	0	0	3 (2.1)	1 (1.5)	4 (1.6)
Gastroenteritis	1 (2.8)	0	3 (2.1)	0	4 (1.6)
Vomiting	0	0	3 (2.1)	0	3 (1.2)
Septic shock	0	0	2 (1.4)	0	2 (0.8)
Upper respiratory tract infection	0	0	2 (1.4)	0	2 (0.8)
Suicidal ideation	0	0	0	2 (3.1)	2 (0.8)
Respiratory distress	0	0	2 (1.4)	0	2 (0.8)

AE=adverse event; BRV=brivaracetam; PT=preferred term; SAE=serious adverse event; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: Serious TEAEs were defined as SAEs that had onset on or after the day of first BRV dose.
Note: n=the number of study participants reporting at least 1 serious TEAE for the specified category of AE.
Note: Percentages were relative to the number of study participants in the SS.
Data source: N01266 CSR Table 12.4.1.1

Overall, a total of 83 study participants (32.3%) experienced serious TEAEs, most frequently in the SOC of Nervous system disorders (41 study participants [16.0%]) (N01266 CSR Table 12.4.1.1). Seizure was the most frequently reported serious TEAE by PT.

There were a total of 5 SAEs considered to be IMP related: weight decreased, epilepsy, seizure, status epilepticus, and homicidal ideation (each experienced by 1 study participant [0.4%]).

CHMP comments

Seizures (6.2%) and status epilepticus (4.3%) were the most common serious TEAEs. The highest proportion of patients with "status epilepticus" were reported in patients ≥1 month to <2 years old (5.6%) and ≥4 to <12 years old (5%).

"Convulsion" is listed as a common ADR in the SmPC. Status epilepticus is not listed in the SmPC.

Discontinuation due to adverse events

Thirty-one study participants (12.1%) had TEAEs that led to permanent discontinuation of IMP (Table 5 8). The most frequently reported TEAEs overall that led to discontinuation of IMP were suicidal ideation (4 study participants) and pneumonia, simple partial seizures, status epilepticus, pregnancy, and circulatory collapse (2 study participants each). Ten of the 31 study participants discontinued due to IMP-related TEAEs.

Table 5-13: AEs leading to discontinuation (SS)

Study participant number/cohort/ gender/age (years)/ race/weight (kg)	AE onset/outcome date (Relative days)/Study Period	AE preferred term	Serious/ Intensity	Relationship to IMP	Outcome
/LTFU/M/	7/+3/Evaluation	Seizure	No/Moderate	Related	Resolved
LTFU/M/	21/28/Evaluation	Homicidal ideation	Yes/Moderate	Related	Resolved
/LTFU/F	783/783/Evaluation	Generalised tonic-clonic seizure	Yes/Mild	Not related	Resolved
/DE/M/	783/+3/Evaluation	Status epilepticus	Yes/Moderate	Not related	Resolved
/LTFU/M/	34/34/Evaluation	Status epilepticus	Yes/Moderate	Related	Resolved
/LTFU/F	135/+1/Evaluation	Fatigue	No/Moderate	Related	Resolved
		Hypotonia	No/Moderate	Related	Resolved
		Somnolence	No/Moderate	Related	Resolved
/LTFU/M/	236/+10/Evaluation	Simple partial seizures	Yes/Severe	Not related	Resolved
/LTFU/M/	177/177/Evaluation	Pneumonia aspiration	Yes/Severe	Not related	Fatal
/LTFU/M/	5/--/Evaluation	Insomnia	No/Mild	Related	Not Resolved
/LTFU/F/	83/83/Evaluation	Suicidal ideation	Yes/Moderate	Not related	Resolved
/LTFU/M/	--/+7/Evaluation	Epilepsy	Yes/Severe	Related	Resolved
/LTFU/M/	363/+1/Evaluation	Acute respiratory insufficiency	Yes/Severe	Not related	Fatal
		Aspiration	Yes/Severe	Not related	Fatal
		Circulatory collapse	Yes/Severe	Not related	Fatal
/LTFU/F/	91/+212/Evaluation	Weight decreased	Yes/Severe	Related	Resolved
/LTFU/F	81/81/Evaluation	Vomiting	No/Moderate	Not related	Resolved
/LTFU/F/	887/+13/Evaluation	Pneumonia	Yes/Severe	Not related	Fatal
		Septic shock	Yes/Severe	Not related	Fatal
/LTFU/M/	277/--/Evaluation	Hepatic enzyme increased	No/Moderate	Related	Not resolved
/LTFU/F/	633/--/Evaluation	Pregnancy	Yes/Moderate	Not related	Not resolved
/LTFU/F/	146/146/Evaluation	Pneumonia	Yes/Severe	Not related	Fatal
/DE/M/ [a]	64/+148/Evaluation	Aggression	Yes/Severe	Not related	Resolved with sequelae
DE/F/	1052/1059/Evaluation	Intentional self-injury	No/Mild	Not related	Resolved

Table 5-13: AEs leading to discontinuation (SS)

Study participant number/cohort/ gender/age (years)/ race/weight (kg)	AE onset/outcome date (Relative days)/Study Period	AE preferred term	Serious/ Intensity	Relationship to IMP	Outcome
	1159/--/Evaluation	Major depression	No/Moderate	Not related	Not resolved
/DE/F/	66/--/Evaluation	Depression	No/Mild	Related	Not resolved
	70/--/Evaluation	Suicidal ideation	No/Mild	Related	Not resolved
LTFU/M/	+1/+1/--	Apnoea	Yes/Severe	Not related	Fatal
/DE/M/[b]	-7/--/Screening	GGT increased	No/Mild	Not related	Resolving
/DE/M/	188/188/Evaluation	Circulatory collapse	Yes/Severe	Not related	Fatal
/LTFU/F/	1601/--/Evaluation	Pregnancy	No/Mild	Not related	Not resolved
/DE/M/	996/--/Evaluation	Astrocytoma, low grade	Yes/Moderate	Not related	Resolving
DE/F/	22/+20/Evaluation	ALT increased	No/Mild	Related	Resolved
		AST increased	No/Moderate	Related	Resolved
		GGT increased	No/Mild	Related	Resolved
/DE/F/	50/64/Evaluation	Suicidal ideation	No/Moderate	Not related	Resolved
/DE/F/	1831/--/Evaluation	Suicidal ideation	No/Mild	Not related	Not resolved
/DE/F/	+1/--/--	Neurocysticercosis	Yes/Mild	Not related	Not resolved
/LTFU/F/	322/+147/Evaluation	Granulocytopenia	No/Mild	Not related	Resolved
/DE/M/	1156/--/Evaluation	Simple partial seizures	No/Moderate	Not related	Not resolved
	--/--/Evaluation	Simple partial seizures	Yes/Moderate	Not related	Not resolved
/DE/M/	2623/2638/Evaluation	Corona virus infection	Yes/Moderate	Not related	Fatal

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; DE=directly enrolled; F=female; GGT=gamma-glutamyltransferase; IMP=investigational medicinal product; LTFU=long-term follow-up; M=male; SS=Safety Set

Note: Relative day numbers with no prefix were days from the first dose +1, '-' prefixed numbers were days before the first dose, '+' prefixed numbers were days since the last dose, -- indicated missing.

[a] Note that for the event of aggression experienced by Study Participant, IMP was withdrawn; however, this study participant is not presented in N01266 CSR Table 12.5.1.1 (as he did not permanently discontinue IMP but did withdraw consent).

[b] The AE of GGT increased for Study Participant was not considered treatment-emergent (and therefore this study participant is not presented in N01266 CSR Table 12.5.1.1.

Data source: N01266 CSR Listing 9.2.5 and N01266 CSR Listing 1.4

CHMP comments

It is noted that according the Table 5-13 "AEs leading to discontinuation (SS)" 33 patients discontinued treatment because of AEs, including 8 fatal cases. Majority of patients were from the LTFU (n=20) and 13 patients were DE. Majority of AEs leading to treatment discontinuation resolved or were resolving (n=22). The AEs which were not resolved after discontinuation of treatment included pregnancy (n=2), suicidal ideation (n=2), depression/major depression (n=2), simple partial seizures (n=2), neurocystirecosis and hepatic enzyme increase.

Hematology

Mean values for the majority of hematology parameters remained within the normal ranges overall and for each age group. Observed changes from Baseline to the Last Value were small and generally similar between age groups.

Overall, the incidences of possibly clinically significant treatment-emergent (PCST) hematology values in the Evaluation Period were generally low (≤10% for any parameter), with the exception of low neutrophils (46 study participants [18.5%]).

Reported TEAEs associated with hematology values were in the SOCs of Blood and lymphatic system disorders or Investigations and included anemia (5 study participants [1.9%]), hypochromic anemia, neutropenia, neutrophil count decreased, white blood cell count decreased (2 study participants [0.8%] each), and eosinophilia, granulocytopenia, immune thrombocytopenic purpura, iron deficiency anemia, lymphadenopathy, pancytopenia, thrombocytopenia, eosinophil count increased, and hemoglobin decreased (1 study participant [0.4%] each).

Blood chemistry

Mean values for the majority of biochemistry parameters remained within the normal ranges overall and for each age group. Observed changes from Baseline to the Last Value were small and generally similar between age groups. Overall, no consistent or clinically relevant treatment related changes in mean or median chemistry values were observed. With the exception of GGT, the incidences of PCST values for liver function parameters were low. Reported PCST blood chemistry values for liver function included high ALT (9 study participants [3.6%]), high AST (4 study participants [1.6%]), high ALP (4 study participants [1.6%]), and high bilirubin (1 study participant [0.4%]).

Endocrinology

Mean values for the endocrinology parameters remained within the normal ranges for the duration of the study overall and for each age group. Mean and/or median endocrinology values occasionally were outside the normal range overall and for individual age groups at visits where the number of study participants for that visit was small or where values for the given parameter were already outside the normal range at Baseline. These changes were not deemed to be clinically significant.

Urinalysis

Urinalysis parameters were generally within normal ranges and there were no mean changes from Baseline to the Last Value during the Evaluation Period and during the Up Titration Period for DE study participants that were considered clinically relevant.

Vital signs

Mean values for the vital signs parameters remained within the normal ranges overall and for each age group. Observed changes from Baseline to the Last Value were small and generally similar between

age groups. Overall, no consistent or clinically relevant treatment related changes in mean or median vital signs values were observed.

ECG findings

At Baseline, the majority of study participants (194 study participants out of 254 [76.4%]) had normal ECG findings; 58 study participants out of 254 (22.8%) had abnormal but not clinically significant ECG findings; and 2 study participants (0.8%) had clinically significant findings. The percentage of study participants with normal and abnormal but not clinically significant ECG findings remained generally consistent over time through the SV.

Pregnancies

There were 2 pregnancies reported by UCB's Patient Safety database (N01266 CSR Listing 9.2.2):

- Study participant LTFU study participant at study entry. Investigational medicinal product was discontinued.
- Study participant LTFU study participant at study entry. Investigational medicinal product was discontinued.

Tanner stage

Apart from slight inconsistencies regarding the staging of the development process in some study participants between individual visits, the individual data are as expected. There is no obvious effect of the drug on the sexual maturation process.

Behavior and cognition

Achenbach CBCL

Mean and median changes from Baseline in CBCL raw scores for both the study participants aged 1½ to 5 years and for ages 6 to 18 years were small in amplitude and generally negative (reflecting slight improvement) or close to 0. In both age groups, the vast majority of study participants had no shift in T score category from Baseline to last evaluation for each Achenbach CBCL subscale (between normal and borderline or clinical range [BCR]).

The proportions of study participants aged 1½ to 5 who were normal at Baseline and remained in the normal range at the 6-month assessment were 82.1% for aggressive behavior, 79.5% for anxious/depressed, 51.3% for attention problems, 69.2% for emotionally reactive, 82.1% for sleep problems, 59.0% for somatic complaints, and 46.2% for withdrawn. The proportions of study participants aged 6 to 18 years who were normal at Baseline and remained in the normal range at the 6-month assessment were 55.2% for aggressive behavior, 62.1% for anxious/depressed, 44.0% for attention problems, 69.8% for rule-breaking behavior, 42.2% for social problems, 57.8% for somatic complaints, 59.5% for thought problems, and 60.3% for withdrawn/depressed.

BRIEF-P/BRIEF

The BRIEF-P was used for study participants ≥2 years to <5 years of age and the BRIEF was used for study participants ≥5 years of age.

Mean and median changes from Baseline in BRIEF-P and BRIEF raw scores were small in amplitude and generally negative (reflecting slight improvement) or close to 0. In both age groups, the vast majority of study participants had no shift in T score category from Baseline to last evaluation for BRIEF-P/BRIEF subscales (between normal and potentially clinically significant [PCS]). Changes that occurred across the BRIEF-P subscales were mostly from PCS to normal. Across the BRIEF subscales, similar proportions of study participants changed from normal to PCS or from PCS to normal.

The proportions of study participants aged ≥2 years to <5 years of age (BRIEF-P) who were normal at Baseline and remained in the normal range at the 6-month assessment were 80.0% for inhibitory self-control, 77.8% for flexibility, 30.0% for emergent metacognition, and 70.0% for global executive composite (GEC). The proportions of study participants aged ≥5 years of age (BRIEF) who were normal at Baseline and remained in the normal range at the 6-month assessment were 48.5% for behavioral regulation, 49.5% for metacognition, and 43.7% for GEC.

Bayley-III scores

Only 1 study participant met the criteria of the Bayley-III assessment.

PedsQL

Mean and median changes from Baseline in parent-reported PedsQL scores were generally positive (reflecting improvement) or close to 0 when negative, with the exception of values at Early Discontinuation, where the mean changes were negative (ranging from -5.1 for school functioning to -2.3 for emotional functioning).

Similarly, for self-reported PedsQL, the mean and median changes from Baseline were generally positive or close to 0 when negative, with the exception of values at Early Discontinuation, where the mean changes for all but 1 score were negative (ranging from -8.2 for physical functioning to 0.2 for social functioning).

Calculated values and change from Baseline in PedsQL scores, by age, parent reported and self reported are provided for the SS in N01266 CSR Table 7.16.2.1 and N01266 CSR Table 7.16.2.2, respectively. No particular trends in calculated values and change from Baseline in PedsQL scores, by age, parent reported and self-reported were observed.

CHMP comments

No clear changes were observed for sexual maturation, cognitive and behavioral functioning as measured by Tanner scale, Achenbach CBCL, BRIEF-P/BRIEF and PedsQL.

Assessment of suicidality

Positive findings on the Columbia-Suicide Severity Rating Scale (C-SSRS) for questions regarding suicidal ideation and suicidal behavior were reported for 13 study participants and 11 study participants, respectively. Of the study participants who had positive responses on the C SSRS, 11 study participants experienced TEAEs of suicidal ideation, 1 study participant experienced a TEAE of suicide attempt, 4 study participants experienced depression, 1 study participant experienced depressed mood, and 3 study participants experienced self-injurious behavior.

No suicide attempts were reported on the C-SSRS during the study.

2.3.2. Discussion on clinical aspects

N01266 was a Phase 3, open-label, single-arm, multicenter, Long-Term Follow-Up (LTFU) study to evaluate the safety and efficacy of BRV in study participants with epilepsy.

The eligible LTFU study participants were enrollment from studies N01263, EP0065, or N01349 (n=137). In addition, a number of eligible patients were directly enrolled (DE) into the study (n=127).

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

A total of 264 study participants had been enrolled and 257 received BRV treatment in N01266 with a mean of 3.2 study-participants years of exposure. The largest group of patients included into the study was 4-12 years old (n=141). Only 6 out of 15 patients in ≥2 to <4 years age group were exposed for more than 18 months. Thus, even after the completion of the study the information regarding long-term exposure in this age group is very limited. At baseline, patients had the most common type of POS - complex partial seizures (56%) and the most common type of PGS seizures were myoclonic seizures (30%).

Due to study design the interpretation of the observed efficacy results is highly uncertain. In patients ≥2 years of age the absolute numbers and percentage of POS were reduced compared to baseline. Other efficacy variables for all study participants ≥2 years of age – absolute and percent change in 28-days adjusted total seizure frequency from Baseline to the end of the Evaluation Period, seizure freedom, proportion of seizure free days during the evaluation period, - are pointing to the same direction as secondary efficacy variables.

Numbers of study participants <2 years of age were very low thus interpretation of the observed efficacy endpoints is difficult.

The most common TEAEs are similar to the ones known for BRV which are described in the SmPC. No new unexpected TEAEs were reported. Seizures (6.2%) and status epilepticus (4.3%) were the most common serious TEAEs. The highest proportion of patients with "status epilepticus" were reported in patients ≥1 month to <2 years old (5.6%) and ≥4 to <12 years old (5%).

There were some discrepancies observed in reported deaths. Seven patients died during the study according to the Table 5-11 "AEs with an outcome of death (SS)". Patients' age ranged from 0.58 to 14 years old. Two patients were directly enrolled (DE) into the study, while remaining were from the LTFU. The relationship to the IMP was considered as not related by the MAH. It is noted that another fatal outcome was presented in the Table 5-13 "AEs leading to discontinuation (SS)". Patient (LTFU/F/8) died from pneumonia on day 81 from the treatment onset. Addition of this patient to the list would make the most common cause of death pneumonia (n=4). The second most common cause of death was circulatory collapse (n=2). Other death causes were reported in single individual patients.

It is also noted that in the Table 5-13 "AEs leading to discontinuation (SS)" 33 patients discontinued treatment because of AEs, including 8 fatal cases. Majority of patients were from the LTFU (n=20) and 13 patients were DE. Majority of AEs leading to treatment discontinuation resolved or were resolving (n=22). The AEs which were not resolved after discontinuation of treatment included pregnancy (n=2), suicidal ideation (n=2), depression/major depression (n=2), simple partial seizures (n=2), neurocysticercosis and hepatic enzyme increase (n=1 each).

No clear changes/trends were observed for sexual maturation, cognitive and behavioral functioning as measured by Tanner scale, Achenbach CBCL, BRIEF-P/BRIEF and PedsQL.

In summary, no new information regarding efficacy of BRV were reported and the safety findings in N01266 were generally consistent with the known safety profile of BRV.

3. Rapporteur's overall conclusion and recommendation

No new efficacy or safety concerns were identified in the study N01266. Safety profile of the paediatric patients who received BRV treatment and completed the N01266 study was in line with the established safety profile of BRV. Therefore, the benefit-risk ratio remains unchanged. No changes in the SmPC are considered necessary.

☒ **Fulfilled:**

No regulatory action required.