Supplementary Materials

Long-term safety and efficacy of adjunctive brivaracetam in pediatric patients with epilepsy: An open-label, follow-up trial

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Supplementary methods

Study visit sequence

- For patients who continued until study end, the evaluation period extended from entry visit until final evaluation visit.
- For patients who discontinued the trial, the evaluation period lasted from entry visit until early discontinuation visit, followed by a maximum 4-week down-titration period, a 2-week safety (drug-free) period, and a final safety visit.

- During the evaluation period, minimal and full evaluation visits evaluation visits were performed alternatively every month during the first 3 months and every 3 months thereafter.
    - At the 12-month mark, and every 12 months thereafter, a yearly evaluation visit (full evaluation visit with additional assessments) was conducted.
    - Minimal evaluation visits occurred at each subsequent year's 3- and 9-month marks, whereas a full evaluation occurred at each year's 6-month mark.

Other exclusion criteria

- LTFU patients were excluded if they had hypersensitivity to BRV or excipients or comparative drugs during the core trial; had poor compliance with the visit schedule or medication intake in the core trial; had a lifetime history of suicide attempt (patients ≥6 years of age) or had suicidal ideation in the past 6 months.
- Direct enrollers were excluded for previous BRV treatment; concomitant use of LEV at screening or in the 4 weeks before screening; epilepsy secondary to a progressive cerebral disease or tumor, or any other progressively neurodegenerative disease; history of primary generalized epilepsy; history of status epilepticus in the month before screening or during the up-titration period; history or presence of pseudoseizures; suffering only from febrile seizures; received felbamate with <18 months of continuous exposure; were treated with vigabatrin and had visual field defects; allergy to pyrrolidone derivatives or investigational product excipients or history of multiple drug allergies; any clinically significant acute or chronic illness; underlying disease or receiving treatment that may interfere with the absorption, distribution, metabolism, and elimination of the trial drug; any medical condition that might interfere with trial participation; a terminal illness; clinically significant deviations from reference range values for laboratory parameters; clinically relevant electrocardiogram (ECG) abnormality; major surgery within 6 months before screening; receipt of any investigational drug or device within 30 days before screening (use of ASMs marketed for adults but not approved for pediatric use was not considered to be investigational

for the purposes of this trial); or lifetime history of suicide attempt or suicidal ideation in the 6 months before screening.

Other variables

- For patients <2 years of age
    - Other variables based on DRC seizure counts included seizure freedom rate over the evaluation period (all seizure types), the proportion of seizure-free days over the evaluation period (all seizure types), the absolute and percent worsening in average daily frequency of all seizures (all seizure types), and a descriptive summary of seizure frequency by visit based on DRC data.
    - Other variables based on EEG data (recorded for at least 24 hours) were the 50% responder rate for focal seizures (percentage of patients with a ≥50% reduction in average daily frequency of focal seizures recorded on EEG), the absolute and percent change in average daily frequency of all seizures (all seizure types), the seizure freedom (rate and proportion), and the absolute and percent worsening of other seizure types.
- For patients ≥2 years of age
    - Other variables based on DRC data were the 50% responder rate for focal seizures (percentage of patients with a ≥50% reduction in focal seizure frequency per 28 days from baseline), the absolute and percent change in total seizure frequency (all seizure types) per 28 days from baseline to the end of the evaluation period, seizure freedom over the evaluation period, and the proportion of seizure-free days over the evaluation period.
- For variables based on seizure assessments, patients who had no seizures at baseline and post-baseline were regarded as “not evaluable” for the responder assessment; percentages for responders were based on evaluable patients only; patients from core trials EP0065 and N01349 did not have appropriate baseline data and were excluded from these analyses.
- Effects on behavior and cognition were assessed with change from baseline in the Achenbach Child Behavior Checklist (CBCL) 1.5–5 score and CBCL 6–18 score (in patients

1.5–5 and 6–16 years of age, respectively; age at BRV initiation in N01266 or core study) and change from baseline in Behavior Rating Inventory of Executive Function (BRIEF)-Preschool Version (BRIEF-P) and BRIEF scores (in patients 2 to <5 and 5–16 years of age, respectively; age at BRV initiation in N01266 or core study). T-score categories for Achenbach CBCL were classified as "normal" (<65) or "borderline or clinical range" (BCR; ≥65), and T-score categories for BRIEF-P/BRIEF were classified as "normal" (<65) or "potential clinical significance" (PCS; ≥65).

- Kaplan-Meier estimated retention on BRV was also assessed.
- Other variables for all patients included physical and neurological examinations, psychiatric and mental status, laboratory tests, ECG, vital signs, body weight, height and head circumference, and plasma concentrations of BRV and phenytoin (if applicable).

Supplementary tables

TABLE S1 Baseline demographics, epilepsy characteristics, and summary of TEAEs by age group (safety set)

Patients	**≥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)**
Age, mean (SD), years	1.1 (0.5)	2.8 (0.6)	7.7 (2.4)	13.8 (1.3)
Male, n (%)	17 (47.2)	10 (66.7)	79 (56.0)	35 (53.8)
Weight, mean (SD), kg	8.4 (2.9)	12.8 (2.6)	27.2 (11.1)	53.7 (21.1)
Seizure category at baseline[a], n (%)				
Focal seizure	18 (50.0)	4 (26.7)	112 (79.4)	51 (78.5)
Primary generalized seizure	14 (38.9)	11 (73.3)	29 (20.6)	14 (21.5)
Uncategorized	4 (11.1)	0 (0)	0 (0)	0 (0)
Incidence of TEAEs[b], n (%)				
Any TEAEs	34 (94.4)	14 (93.3)	132 (93.6)	60 (92.3)
Serious TEAEs	14 (38.9)	8 (53.3)	42 (29.8)	19 (29.2)
Severe TEAEs	11 (30.6)	6 (40.0)	21 (14.9)	6 (9.2)
Drug-related TEAEs	7 (19.4)	7 (46.7)	46 (32.6)	19 (29.2)
Drug-related serious TEAEs	1 (2.8)	0 (0)	3 (2.1)	1 (1.5)
TEAEs leading to discontinuation	4 (11.1)	5 (33.3)	15 (10.6)	7 (10.8)
Deaths	2 (5.6)	2 (13.3)	2 (1.4)	1 (1.5)
TEAEs[c] reported by ≥10% of all patients, n (%)				
Nasopharyngitis	11 (30.6)	4 (26.7)	44 (31.2)	16 (24.6)
Pyrexia	15 (41.7)	5 (33.3)	38 (27.0)	7 (10.8)

Pharyngitis	10 (27.8)	2 (13.3)	39 (27.7)	8 (12.3)
Vomiting	11 (30.6)	5 (33.3)	35 (24.8)	4 (6.2)
Upper respiratory tract infection	10 (27.8)	5 (33.3)	23 (16.3)	8 (12.3)
Seizure	3 (8.3)	3 (20.0)	24 (17.0)	12 (18.5)
Headache	0 (0)	1 (6.7)	22 (15.6)	16 (24.6)
Diarrhea	7 (19.4)	0 (0)	21 (14.9)	8 (12.3)
Pharyngotonsillitis	5 (13.9)	0 (0)	21 (14.9)	10 (15.4)
Cough	6 (16.7)	2 (13.3)	19 (13.5)	5 (7.7)
Gastroenteritis	8 (22.2)	0 (0)	18 (12.8)	5 (7.7)
Decreased appetite	6 (16.7)	1 (6.7)	16 (11.3)	7 (10.8)
Influenza	5 (13.9)	2 (13.3)	16 (11.3)	6 (9.2)
Bronchitis	7 (19.4)	3 (20.0)	16 (11.3)	2 (3.1)
Somnolence	3 (8.3)	1 (6.7)	17 (12.1)	6 (9.2)
Serious TEAEs[c] reported by ≥3 patients				
Seizure	1 (2.8)	1 (6.7)	12 (8.5)	2 (3.1)
Status epilepticus	2 (5.6)	0 (0)	7 (5.0)	2 (3.1)
Pneumonia	3 (8.3)	0 (0)	4 (2.8)	1 (1.5)
Pyrexia	2 (5.6)	1 (6.7)	3 (2.1)	0 (0)
Dehydration	1 (2.8)	0 (0)	3 (2.1)	1 (1.5)
Epilepsy	1 (2.8)	0 (0)	4 (2.8)	0 (0)
Generalized tonic-clonic seizure	1 (2.8)	1 (6.7)	2 (1.4)	1 (1.5)
Gastroenteritis	1 (2.8)	0 (0)	3 (2.1)	0 (0)
Somnolence	0 (0)	0 (0)	3 (2.1)	1 (1.5)

Vomiting	0 (0)	0 (0)	3 (2.1)	0 (0)

Abbreviations: SD, standard deviation; TEAE, treatment-emergent adverse event.
[a]Seizure category at baseline according to SAP section 3.10.3.
[b]Each patient is counted at most once for each category.
[c]Medical Dictionary for Regulatory Activities Version 18.1 Preferred Term (Version 18.1 was the most recent version at the start of the trial and terms may have changed over time).

TABLE S2 Summary of epileptic syndrome classifications

Patients, n (%)	**Patients with focal seizures (*n* = 185)**	**Patients with primary generalized seizures (*n* = 68)**	**All patients (*n* = 257)**
Seizure type			
Localized	163 (88.1)	10 (14.7)	173 (67.3)
Generalized	9 (4.9)	54 (79.4)	65 (25.3)
Undetermined	7 (3.8)	15 (22.1)	22 (8.6)
Etiology reported by ≥5% of all patients			
Idiopathic	6 (3.2)	19 (27.9)	25 (9.7)
Cryptogenic or Symptomatic	160 (86.5)	34 (50.0)	195 (75.9)
Symptomatic	6 (3.2)	14 (20.6)	21 (8.2)
Syndrome reported by ≥5% of all patients			
Temporal lobe epilepsy	70 (37.8)	6 (8.8)	76 (29.6)
Frontal lobe epilepsy	91 (49.2)	4 (5.9)	95 (37.0)
Occipital lobe epilepsy	19 (10.3)	0	19 (7.4)
Parietal lobe epilepsy	18 (9.7)	0	18 (7.0)

The percentages may add to more than 100% as subject may be represented in more than one category. Four patients are included in “All patients” only as they cannot be categorized into seizure categories.

Table S3 Narrative summary of deaths with reported TEAEs

Age (years)	AE onset date (relative day)	AE outcome date (relative day)	Seizure category	Summary
1.75	July 17, 2013(363)	July 18, 2013 (+1)	PGS	Patient diagnosed with acute respiratory failure, aspiration from non-food item, and circulatory failure. Study treatment was withdrawn, followed by prolonged hospitalization.
0.58	July 15, 2013 (146)	July 15, 2013 (146)	PGS	Patient diagnosed with pneumonia (community-acquired). Study treatment was withdrawn, concomitant medication was administered, followed by prolonged hospitalization.
2.25	October 2, 2019 (177)	October 2, 2019 (177)	PGS	Patient diagnosed with aspiration pneumonia. Study treatment was withdrawn, followed by prolonged hospitalization.
2.17	January 7, 2018 (+1)	January 7, 2018 (+1)	PGS	Patient diagnosed with apnea. Study treatment was withdrawn.
4.08	October 18, 2014 (887)	November 2, 2014 (+13)	Focal	Patient diagnosed with pneumonia (community-acquired) and septic shock. Study treatment was withdrawn, concomitant medications were administered, followed by prolonged hospitalization.
8.50	August 7, 2021 (2623)	August 22, 2021 (2638)	Focal	Patient diagnosed with COVID-19 infection, which caused COVID-19 pneumonia. Study treatment was withdrawn, concomitant medications were administered, followed by prolonged hospitalization.
14.00	September 6, 2014 (188)	September 6, 2014 (188)	Focal	Patient was diagnosed with circulatory collapse. Study treatment was withdrawn.

Abbreviations: AE, adverse event; COVID-19, coronavirus (SARS-CoV-2) disease 2019; PGS, primary generalized seizure; TEAEs, treatment-emergent adverse events.

Medical Dictionary for Regulatory Activities Version 18.1 Preferred Term (Version 18.1 was the most recent version at the start of the trial and terms may have changed over time). Relative day numbers with no prefix are days from first dose +1, "+" prefixed numbers are days since last dose.

TABLE S4 Change from baseline to last evaluation for each Achenbach CBCL 1.5–5 score and CBCL 6–18 score in patients with focal seizures (safety set)

	n	**Mean (SD)**
Achenbach CBCL 1.5-5		
Aggressive behavior	32	−1.4 (7.3)
Anxious/depressed	32	−1.5 (2.4)
Attention problems	32	−0.5 (2.3)
Emotionally reactive	32	−1.0 (4.1)
Sleep problems	32	−1.1 (3.0)
Somatic complaints	32	−0.9 (2.5)
Withdrawn	32	−0.7 (3.4)
Other problems	32	−3.2 (6.9)
Achenbach CBCL 6-18		
Aggressive behavior	102	−1.9 (5.2)
Anxious/depressed	102	−1.5 (3.7)
Attention problems	102	−1.4 (3.9)
Rule-breaking behavior	102	−0.6 (2.5)
Social problems	102	−0.9 (3.6)
Somatic complaints	102	−1.0 (3.1)
Thought problems	102	−0.7 (3.6)
Withdrawn/depressed	102	−0.0 (2.7)

Abbreviations: CBCL, Child Behavior Checklist; SD, standard deviation.
Only included patients with baseline and at least one post-baseline result from the CBCL 1.5-5 questionnaire or 6-18 questionnaire. T-scores were not calculated at any visit where more than eight responses were missing from the CBCL 1.5-5 questionnaire or 6-18 questionnaire. Baseline is obtained from the core study screening visit. Negative scores indicate improvement.

TABLE S5 Change from baseline to last evaluation for the subscale scores for the BRIEF-P questionnaire and BRIEF questionnaire in patients with focal seizures (safety set)

	n	**Mean (SD)**
BRIEF-P		
Inhibit	7	−6.6 (6.4)
Shift	7	−2.1 (2.1)
Emotional control	7	−4.9 (4.7)
Working memory	7	−4.0 (7.8)
Plan/organize	7	−3.0 (5.4)
BRIEF		
Inhibit	101	−1.5 (5.2)
Shift	101	−0.3 (3.5)
Emotional control	101	−0.8 (4.6)
Initiate	101	−0.5 (3.8)
Working memory	101	−1.7 (4.5)
Plan/organize	101	−1.3 (5.7)
Organization of materials	101	−0.6 (3.1)
Monitor	101	−0.6 (4.1)

Abbreviations: BRIEF, Behavior Rating Inventory of Executive Function; BRIEF-P, BRIEF-Preschool Version; SD, standard deviation.

Only included patients with baseline and at least one post-baseline result from the BRIEF-P questionnaire or BRIEF questionnaire. T-scores were not calculated for any index where responses to one or more constituent items were missing. Baseline is obtained from the core study screening visit. Negative scores indicate improvement.

TABLE S6 Change in 28-day adjusted frequency (DRC data) and average daily frequency (EEG data) of all seizures from baseline to the end of the evaluation period (full analysis set)

	Mean baseline	Absolute change		Percent change	
	ASF/ADF	*n*	Median (min, max)	*n*	Median (min, max)
DRC data					
Patients <2 years of age	445.13	22	48.45 (−19.8, 3240.7)	22	87.72 (−29.1, 100.0)
Patients <2 years of age with focal seizures	384.58	10	39.60 (32.7, 1248.1)	10	96.86 (45.4, 100.0)
Patients ≥2 years of age	90.27	167	16.86 (−7075.3, 680.0)	139	60.32 (−693.7, 100.0)
Patients ≥2 years of age with focal seizures	62.42	134	7.09 (−7075.3, 680.0)	106	63.00 (−693.7, 100.0)
EEG data					
Patients <2 years of age	3.86	14	0 (−5.0, 20.7)	7	98.41 (−250.0, 100.0)
Patients <2 years of age with focal seizures	2.75	8	0.50 (0, 12.5)	4	100.00 (96.2, 100.0)

Abbreviations: ADF, average daily frequency; ASF, adjusted seizure frequency; DRC, daily record card; EEG, electroencephalogram.
Patients from core trials EP0065 and N01349 did not have appropriate baseline data and were excluded from these analyses. No data were available for patients ≥2 years of age based on EEG data. Change is defined as decrease in 28-day ASF compared with baseline or decrease in ADF compared with baseline. Because percent change cannot be calculated for patients with 0 seizures at baseline, the n values for absolute change and percent change may differ.

TABLE S7 Responder rates of all seizures and focal seizures from baseline for the subset of patients with seizures at baseline

	All seizures		Focal seizures	
	N_{ev}	*n* (%)	N_{ev}	*n* (%)
DRC data				
Patients <2 years of age	22	15 (68.2)	12	10 (83.3)
Patients <2 years of age with focal seizures	10	9 (90.0)	10	9 (90.0)
Patients ≥2 years of age	139	81 (58.3)	115	65 (56.5)
Patients ≥2 years of age with focal seizures	106	61 (57.5)	105	60 (57.1)
EEG data				
Patients <2 years of age	7	6 (85.7)	5	5 (100)
Patients <2 years of age with focal seizures	4	4 (100)	3	3 (100)

Abbreviations: DRC, daily record card; EEG, electroencephalogram; N_{ev}, number of evaluable patients.
Response is defined as a ≥50% reduction in 28-day adjusted focal seizure frequency (DRC) and in average daily frequency (EEG) compared with baseline. Evaluable patients had at last one seizure at baseline and post-baseline. Patients from core trials EP0065 and N01349 did not have appropriate baseline data and were excluded from these analyses. No data were available for patients ≥2 years of age based on EEG data.

TABLE S8 Proportion of seizure-free days during the evaluation period based on DRC data (full analysis set)

	n	Mean (SD)	Median (min, max)
Patients <2 years			
All patients	36	0.69 (0.37)	0.92 (0, 1.00)
Patients with focal seizures	18	0.78 (0.35)	0.96 (0.03, 1.00)
Patients ≥2 years			
All patients	208	0.70 (0.33)	0.83 (0.01, 1.00)
Patients with focal seizures	157	0.76 (0.30)	0.90 (0.01, 1.00)

Abbreviation: DRC, daily record card.
Proportion of seizure-free days is the number of days with no seizures on DRC data/number of days of recorded DRC data.

TABLE S9 Worsening in 28-day adjusted frequency (DRC data) and average daily frequency (EEG data) of primary generalized seizures from baseline to the end of the evaluation period (full analysis set)

	Mean baseline	Absolute worsening		Percent worsening	
	ASF/ADF	*n*	Median (min, max)	*n*	Median (min, max)
DRC data					
Patients <2 years of age	445.13	22	−48.45 (−3240.7, 19.8)	22	−87.72 (−100.0, 29.1)
Patients <2 years of age with focal seizures	384.58	10	−39.60 (−1248.1, −32.7)	10	−96.86 (−100.0, −45.4)
EEG data					
Patients <2 years of age	0.21	14	0 (−1.0, 5.0)	2	75.00 (−100.0, 250.0)
Patients <2 years of age with focal seizures	0.13	8	0 (−1.0, 0)	1	−100.0 (−100.0, −100.0)

Abbreviations: ADF, average daily frequency; ASF, adjusted seizure frequency; DRC, daily record card; EEG, electroencephalogram.
No data were available for patients ≥2 years of age. Patients from core trials EP0065 and N01349 did not have appropriate baseline data and were excluded from these analyses. Worsening is defined as increase in 28-day ASF (DRC data) or increase in ADF of seizures (EEG data) compared with baseline. Because percent worsening cannot be calculated for patients with 0 ASF/ADF at baseline, the n values for absolute worsening and percent worsening may differ. Negative data for worsening indicate a reduction of seizure frequency in these analyses.

Co-investigator appendix

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