Electronic Supplementary Material

Safety and Tolerability of Adjunctive Brivaracetam in Pediatric Patients < 16 Years with Epilepsy: An Open-Label Trial

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Table S1 Baseline demographic and epilepsy characteristics (safety set)

	Age group		
	1 month to < 2 years (*n* = 30)	2 to < 12 years (*n* = 51)	12 to < 16 years (*n* = 18)
Age, median (min, max), years	1.3 (0.2, 1.9)	5.9 (2.1, 11.9)	13.7 (12.1, 15.6)
Weight, median (min, max), kg	9.1 (3.6, 15.2)	21.0 (9.5, 55.9)	46.5 (36.0, 75.0)
BMI, mean (SD), kg/m^2	16.1 (2.7)	16.8 (3.5)	19.8 (2.9)
Male, *n* (%)	15 (50.0)	26 (51.0)	7 (38.9)
Race, *n* (%)			
White	22 (73.3)	42 (82.4)	15 (83.3)
Black	0	3 (5.9)	1 (5.6)
Asian	0	0	0
Other	8 (26.7)	6 (11.8)	2 (11.1)
Seizure type,[a] *n* (%)			
Focal seizures	14 (46.7)	26 (51.0)	10 (55.6)
Primary generalized seizures	16 (53.3)	25 (49.0)	8 (44.4)
Baseline seizure days,[b] mean (SD)	20.0 (10.0)	15.1 (11.3)	12.0 (10.9)
Number of prior AEDs, *n* (%)			
0–1	19 (63.3)	12 (23.5)	6 (33.3)
2–4	10 (33.3)	15 (29.4)	7 (38.9)
≥ 5	1 (3.3)	24 (47.1)	5 (27.8)
Number of concomitant AEDs, (%)			
1	12 (40.0)	15 (29.4)	5 (27.8)
2	15 (50.0)	19 (37.3)	7 (38.9)
3	3 (10.0)	17 (33.3)	6 (33.3)
Most frequently used concomitant AEDs (≥ 10% of all patients)			
Valproic acid	17 (56.7)	24 (47.1)	10 (55.6)

Topiramate	7 (23.3)	18 (35.3)	2 (11.1)
Lamotrigine	1 (3.3)	11 (21.6)	5 (27.8)
Clobazam	4 (13.3)	8 (15.7)	2 (11.1)
Phenobarbital	10 (33.3)	3 (5.9)	1 (5.6)
Oxcarbazepine	3 (10.0)	4 (7.8)	6 (33.3)
Epilepsy duration, mean (SD), years	0.7 (0.4)	4.1 (2.7)	8.0 (4.8)
Age at time of first seizure, mean (SD), years	0.5 (0.4)	2.6 (2.8)	5.8 (4.4)
Epileptic syndrome,[c] *n* (%)			
Localization-related	15 (50.0)	26 (51.0)	10 (55.6)
Idiopathic	1 (3.3)	1 (2.0)	0
Cryptogenic or symptomatic	14 (46.7)	25 (49.0)	10 (55.6)
Generalized	11 (36.7)	21 (41.2)	8 (44.4)
Idiopathic	1 (3.3)	6 (11.8)	5 (27.8)
Cryptogenic or symptomatic	7 (23.3)	10 (19.6)	3 (16.7)
Symptomatic	3 (10.0)	7 (13.7)	0
Undetermined[d]	7 (23.3)	6 (11.8)	0
Generalized and focal features	1 (3.3)	5 (9.8)	0
Other[e]	6 (20.0)	1 (2.0)	0
Special syndromes	1 (3.3)	3 (5.9)	0
Situation-related seizures	0	3 (5.9)	0

AED antiepileptic drug, *BMI* body mass index, *max* maximum value, *min* minimum value, *SD* standard deviation

[a]Seizure type was defined as follows: focal seizures included individuals with a history of only Type I seizures at baseline. The category for primary generalized seizures included individuals with Type II seizures or mixed seizure disorders

[b]Mean number of seizure days standardized to a 28-day duration, during the observed baseline period

[c]Patients could be classified into multiple categories

[d]Epilepsies and syndromes undetermined as focal or generalized

[e]Other indeterminate epilepsies without unequivocal focal or generalized features

Table S2 Incidence of TEAEs and drug-related TEAEs reported by ≥ 3% of all patients (safety set)

n (%)	Age group		
	1 month to < 2 years (*n* = 30)	2 to < 12 years (*n* = 51)	12 to < 16 years (*n* = 18)
At least one TEAE	24 (80.0)	31 (60.8)	11 (61.1)
TEAEs (MedDRA Version 15.0 Preferred Term) reported by ≥ 3 of all patients			
Convulsion	5 (16.7)	3 (5.9)	2 (11.1)
Somnolence	2 (6.7)	3 (5.9)	3 (16.7)
Pyrexia	7 (23.3)	1 (2.0)	0
Irritability	5 (16.7)	2 (3.9)	1 (5.6)
Decreased appetite	3 (10.0)	3 (5.9)	1 (5.6)
Pharyngotonsillitis	4 (13.3)	1 (2.0)	0
Fatigue	0	3 (5.9)	2 (11.1)
Dehydration	4 (13.3)	0	0
Diarrhea	3 (10.0)	1 (2.0)	0
Otitis media	2 (6.7)	2 (3.9)	0
Psychomotor hyperactivity	0	4 (7.8)	0
Aggression	0	2 (3.9)	2 (11.1)
Headache	0	2 (3.9)	1 (5.6)
At least one drug-related TEAE[a]	5 (16.7)	21 (41.2)	6 (33.3)
Drug-related TEAEs (MedDRA Version 15.0 Preferred Term) reported by ≥ 3% of all patients			
Somnolence	1 (3.3)	3 (5.9)	3 (16.7)
Decreased appetite	2 (6.7)	3 (5.9)	1 (5.6)
Fatigue	0	3 (5.9)	1 (5.6)

Irritability	0	2 (3.9)	1 (5.6)
Psychomotor hyperactivity	0	3 (5.9)	0
Aggression	0	2 (3.9)	1 (5.6)

MedDRA Medical Dictionary for Regulatory Activities, *TEAE* treatment-emergent adverse event

Note: *n* = number of patients reporting a TEAE for the combined evaluation, down-titration, and safety periods. Percentages are relative to the number of patients in the safety set

[a]Adverse events were considered related to the trial drug if either the relationship to trial drug was specified as related by the investigator, or if the relationship to trial drug was not specified

Table S3 Trough concentrations of brivaracetam and its metabolites during the evaluation period (pharmacokinetic per-protocol set)

	Trough plasma concentration (µg/mL)[a], geometric mean (geometric CV%)		
	1 month to < 2 years	2 to < 12 years	12 to < 16 years
End of first dosing week[b] – Visit 3	(*n* = 18)	(*n* = 27)	(*n* = 11)
Brivaracetam	0.206 (86.0)	0.214 (66.7)	0.300 (134.2)
BRV-OH	0.059 (67.0)	0.068 (42.3)	0.045 (34.9)
BRV-OHAC	0.005 (42.4)	0.007 (48.3)	0.008 (46.6)
BRV-AC	0.009 (103.8)	0.014 (102.2)	0.018 (100.8)
End of second dosing week[c] – Visit 4	*n* = 15	*n* = 24	*n* = 4
Brivaracetam	0.343 (80.1)	0.451 (64.4)	0.530 (46.5)
BRV-OH	0.124 (61.1)	0.121 (57.0)	0.126 (18.8)
BRV-OHAC	0.011 (37.3)	0.013 (41.9)	0.018 (14.7)
BRV-AC	0.017 (92.2)	0.027 (79.6)	0.039 (61.1)
End of third dosing week[d] – Visit 5	*n* = 12	*n* = 22	*n* = 4
Brivaracetam	0.596 (138.0)	0.827 (65.8)	1.065 (36.8)
BRV-OH	0.222 (79.1)	0.274 (49.5)	0.225 (20.0)
BRV-OHAC	0.018 (64.2)	0.025 (44.4)	0.034 (31.0)
BRV-AC	0.027 (163.5)	0.055 (75.3)	0.086 (55.1)

[a]Multiply by 4.713646 to convert concentrations from µg/mL to µmol/L. Metabolite concentrations are expressed in brivaracetam-equivalents and use the same conversion factor

[b]Low dose

[c]Mid dose

[d]High dose

BRV-AC acid metabolite of brivaracetam, *BRV-OH* hydroxy metabolite of brivaracetam, *BRV-OHAC* hydroxy acid metabolite of brivaracetam, *CV* coefficient of variation

Table S4 Seizure days (full analysis set)

	Patients with focal seizures[a]		
	1 month to < 2 years (*n* = 14)	2 to < 12 years (*n* = 25)	12 to < 16 years (*n* = 9)
Number of seizure days,[b] median			
Baseline period	19.7	8.0	0.0
Evaluation period	14.6	4.0	2.7
Absolute reduction from baseline in number of seizure days, median	4.0	0.0	0.0
Percent reduction from baseline in number of seizure days,[c] median	23.7	4.8	1.4
	Patients with primary generalized seizures[d]		
	1 month to < 2 years (*n* = 16)	2 to < 12 years (*n* = 25)	12 to < 16 years (*n* = 8)
Number of seizure days,[b] median			
Baseline period	26.0	20.0	17.3
Evaluation period	22.5	24.0	10.0
Absolute reduction from baseline in number of seizure days, median	0.6	0.0	4.0
Percent reduction from baseline in number of seizure days,[e] median	4.2	0.0	23.8

[a]Patients with a history of focal seizures with or without secondary generalization and no primary generalized seizures at baseline

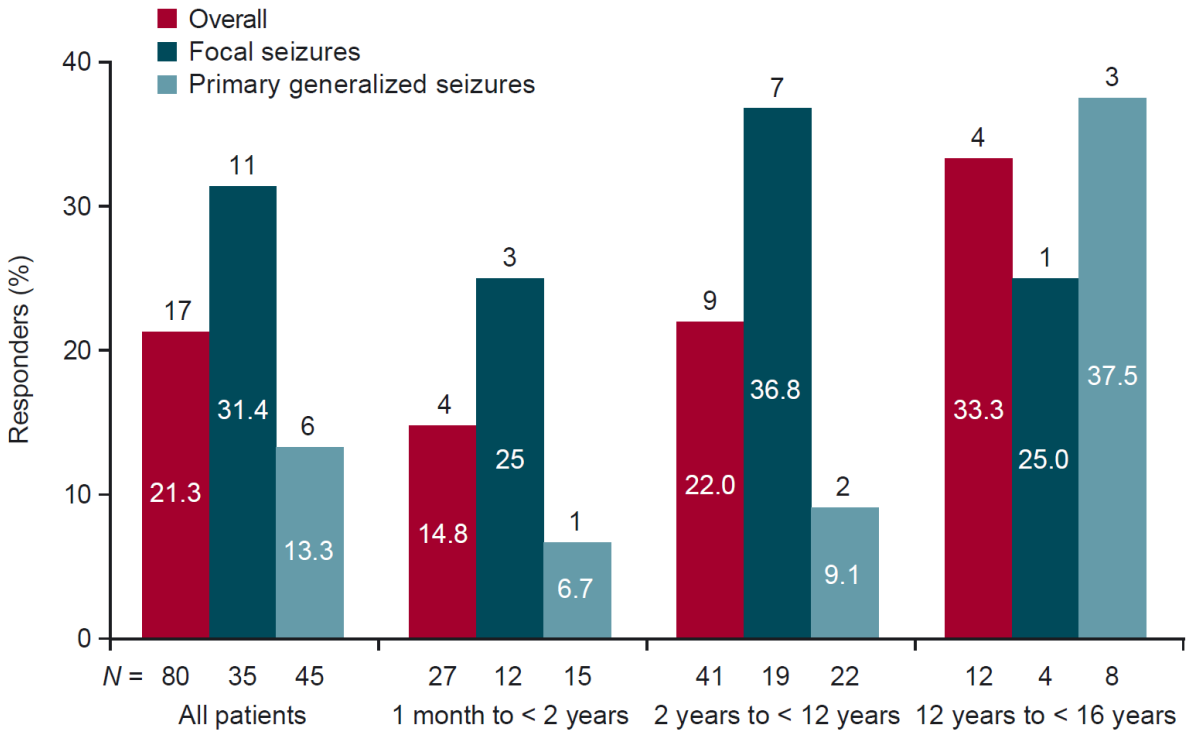
[b]Number of seizure days, standardized to a 28-day duration

[c]Patients with a zero seizure count during the baseline period (*n* = 13) were excluded from the percent reduction analysis as percent change from baseline could not be calculated

[d]Patients with a history of primary generalized seizures at baseline; patients could also have had focal seizures

[e]Patients with a zero seizure count during the baseline period (*n* = 4) were excluded from the percent reduction analysis as percent change from baseline could not be calculated

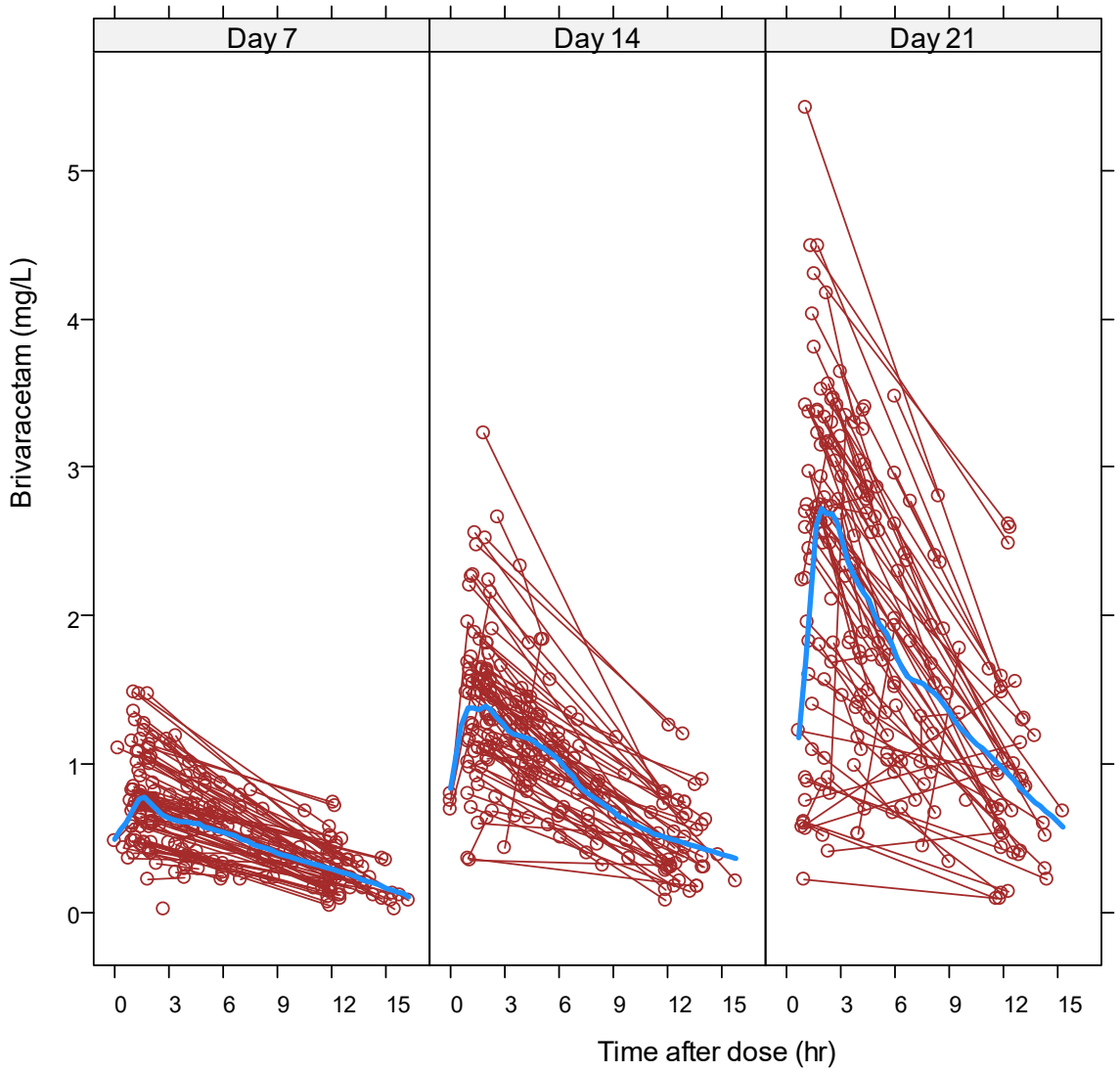
Fig. S1 Responder rate based on a ≥ 50% reduction in seizure days from the baseline period to the end of the evaluation period, according to seizure diary data overall, and by age and seizure category (FAS population)



FAS full analysis set

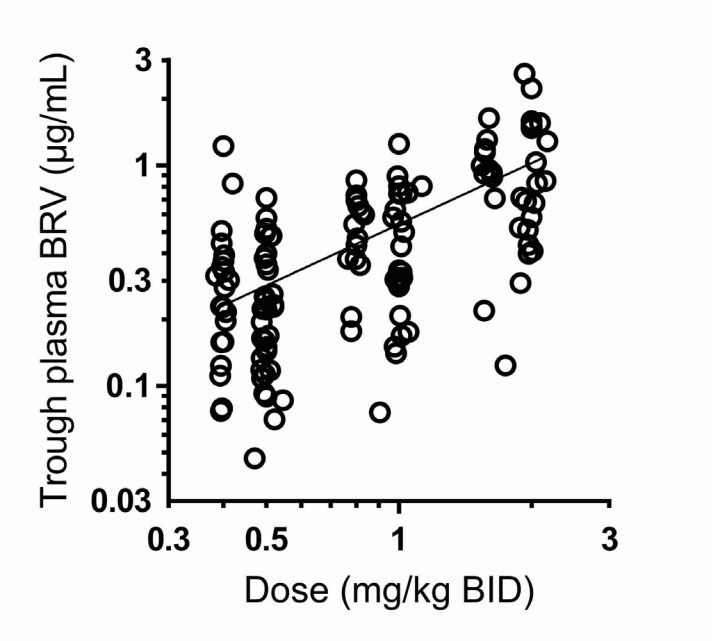
Note: Patients with a zero seizure count during the baseline period were excluded from the analysis as percent change from baseline could not be calculated. Numbers above bars represent the number of patients who responded to treatment.

Fig. S2 Individual plasma concentration versus time profiles for brivaracetam at the low (Day 7), mid (Day 14), and high (Day 21) dose levels



Blue lines are Loess smoothing curves

Fig. S3 Predose plasma brivaracetam concentration versus mg/kg dose in the overall population



BID twice daily, *BRV* brivaracetam