Long-Term Efficacy and Tolerability of Brivaracetam in Pediatric Patients With Focal-Onset Seizures and Cognitive or Learning Comorbidities: Post Hoc Analysis of an Open-Label Trial

Poster P818

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Overview

QUESTION

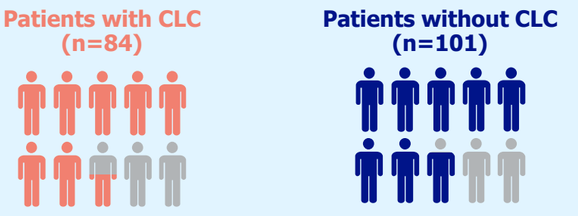
What is the long-term retention, efficacy, and tolerability of adjunctive brivaracetam (BRV) in pediatric patients with focal-onset seizures with or without cognitive or learning comorbidities (CLC)?

INVESTIGATION

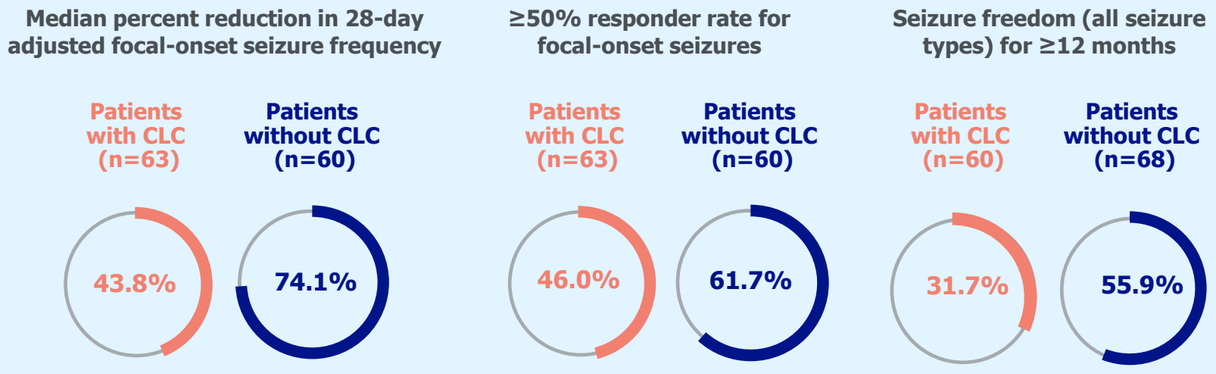
Post hoc analysis of a Phase III, open-label, follow-up trial (N01266, NCT01364597). Subgroup analyses were performed for patients with and without ongoing CLC at baseline.

RESULTS

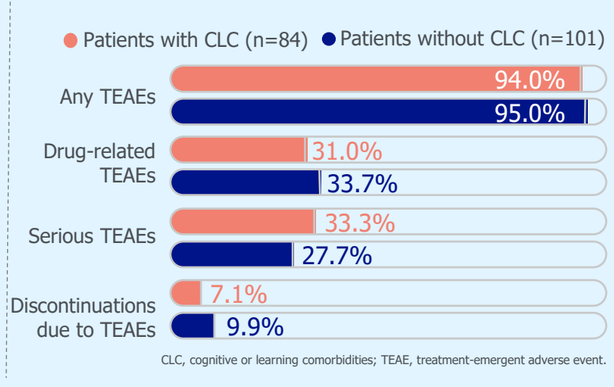
Kaplan-Meier estimated BRV treatment retention



Efficacy (patients >2 years of age)



Tolerability



CLC, cognitive or learning comorbidities; TEAE, treatment-emergent adverse event.

CONCLUSIONS

In this analysis, pediatric patients with focal-onset seizures and ongoing CLC were generally more difficult to treat than those without CLC. Although the observed efficacy response was numerically lower in patients with vs without CLC, it still indicated a clinically relevant seizure frequency reduction. The incidences of treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious TEAEs, and discontinuations due to TEAEs during long-term BRV treatment were similar in patients with and without CLC. These data indicate that BRV could be an efficacious and well-tolerated treatment option for pediatric patients with and without CLC.

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Background

- Brivaracetam (BRV) is indicated for the treatment of focal-onset seizures in patients ≥1 month of age in the United States,[1] and as adjunctive therapy for the treatment of focal-onset seizures with or without secondary generalization in patients ≥2 years of age with epilepsy in the European Union.[2]
- Cognitive and learning comorbidities are common in children with epilepsy. [3]

Objective

- To evaluate long-term efficacy and tolerability of adjunctive BRV in pediatric patients with focal-onset seizures with or without cognitive or learning comorbidities (CLC).

Methods

TRIAL DESIGN

- N01266 (ClinicalTrials.gov: NCT01364597) was a Phase III, open-label, single-arm, multicenter, long-term trial that evaluated the long-term safety, tolerability, and efficacy of BRV as adjunctive treatment in children with epilepsy.
  - Patients who enrolled from a core BRV trial (ie, long-term follow-up patients from N01263, EP0065, or N01349) must have been ≥1 month to <16 years of age upon entry into the core trial; eligible patients who had focal-onset seizures and enrolled in N01266 without having participated in a core trial (ie, direct enrollers) must have been ≥4 to <17 years of age.
  - Patients received a maximum of 5 mg/kg/day BRV as tablet or oral solution (max dose ≤200 mg/day).

ANALYSIS

- Post hoc subgroup analysis of patients with focal-onset seizures with or without ongoing CLC[a] at baseline.
- Safety Set (SS): all patients with focal-onset seizures who enrolled and took at least one dose of BRV in this trial.
- Full Analysis Set (FAS): all patients in the SS who were >2 years of age and had at least one completed post-baseline daily record card (documenting seizure occurrence).
- Assessed outcomes: BRV treatment retention, efficacy in patients >2 years of age (median percent reduction in focal-onset seizure frequency from baseline to the end of the evaluation period, ≥50% responder rate for focal-onset seizures [responders were defined as having ≥50% reduction in seizure frequency compared with baseline], and ≥12 months continuous seizure freedom from all seizure types at any time during the evaluation period), and tolerability.

[a]Patients with CLC were defined by PT for ongoing cognitive or learning comorbidities (attention deficit/hyperactivity disorder, autism, autism spectrum disorder, developmental delay, disturbance in attention, dyscalculia, dysgraphia, dyslexia, encephalopathy, encephalopathy neonatal, language disorder, learning disability, learning disorder, mental disability, mental impairment, mental retardation, mild mental retardation, moderate mental retardation, neurodevelopmental disorder, severe mental retardation, speech disorder, speech disorder developmental) or PT for ongoing comorbidities associated with cognitive or learning disabilities (Aicardi's syndrome, Angelman's syndrome, double cortex syndrome, Kabuki make-up syndrome, Lennox-Gastaut syndrome, lissencephaly, polymicrogyria, severe myoclonic epilepsy of infancy, trisomy 21). CLC, cognitive or learning comorbidities; PT, preferred term.

Results

BASELINE DEMOGRAPHICS

- A total of 257 patients received at least one dose of BRV in this trial.
- Of 185 patients with focal-onset seizures (SS), 84 (45.4%) had ongoing CLC at baseline.
- The most common CLC were:
  - Developmental delay 27 (14,6 %)
  - Attention deficit/hyperactivity disorder 20 (10,8 %)
  - Mental retardation (intellectual disability) 13 (7,0 %).

Baseline demographics and epilepsy characteristics (SS)

	PATIENTS WITH CLC (n=84)	PATIENTS WITHOUT CLC (n=101)
Age, mean (SD), years	9.2 (4.1)	8.3 (4.5)
Male, n (%)	56 (66.7)	51 (50.5)
Weight, mean (SD), kg	34.2 (21.7)	31.8 (18.8)
Epilepsy duration, mean (SD), years	6.2 (3.8)	4.3 (3.7)
Age at diagnosis, mean (SD), years	3.1 (3.0)	4.0 (3.5)
Focal-onset seizure category at baseline[a,b], n (%)		
Simple partial seizures (*focal aware*)	19 (22.6)	48 (47.5)
Complex partial seizures (*focal impaired awareness*)	63 (75.0)	66 (65.3)
Partial evolving to secondary generalized (*focal to bilateral tonic-clonic*)	47 (56.0)	52 (51.5)
Prior and ongoing medical conditions[c,d] reported by ≥20% of patients in either subgroup, n (%)		
Any medical conditions	84 (100)	84 (83.2)
Nervous system disorders	66 (78.6)	39 (38.6)
Psychiatric disorders	42 (50.0)	13 (12.9)
Congenital, familial, and genetic disorders	37 (44.0)	25 (24.8)
General disorders and administration site conditions	31 (36.9)	3 (3.0)
Infections and infestations	29 (34.5)	32 (31.7)
Gastrointestinal disorders	25 (29.8)	13 (12.9)
Respiratory, thoracic, and mediastinal disorders	19 (22.6)	17 (16.8)
Eye disorders	18 (21.4)	8 (7.9)

[a]4 patients with cognitive and learning comorbidities and 3 patients without had 'epilepsies and syndromes undetermined whether focal or generalized', 7 patients with cognitive and learning comorbidities and 2 patients without had 'generalized epilepsies'; [b]Patients could have had more than one type of seizure at baseline; [c]Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 System Organ Class; [d]Includes both resolved and ongoing medical conditions at the day of first BRV dose in the core trials for long-term follow-up patients or at the day of first BRV dose in N01266 for direct enrollers. CLC, cognitive or learning comorbidities.

- Patients with CLC were more commonly male and had a longer mean epilepsy duration; a numerically higher proportion had prior/ongoing comorbid conditions (most commonly neurological or psychiatric) and had used ≥5 prior ASMs.

PATIENTS DISPOSITION

- Overall, 44 (52.4%) patients with CLC and 50 (49.5%) without CLC completed the trial.
  - The most common reasons for discontinuation (≥10% of patients) were lack of efficacy (16.7%) and consent withdrawn (14.3%) in the CLC group, and lack of efficacy (12.9%) and other (13.9%) in patients without CLC.

EXPOSURE

- The median BRV treatment duration was 35.4 months in both subgroups.
- The median BRV modal dose was 3.7 mg/kg/day in patients with CLC and 4.0 mg/kg/day in patients without CLC.

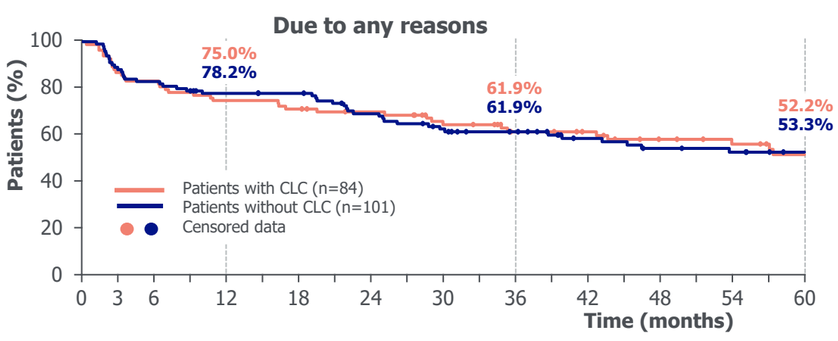
Prior and concomitant ASMs (SS)

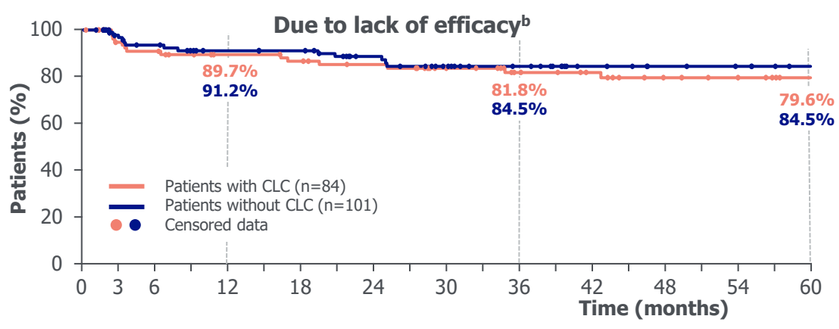
	PATIENTS WITH CLC (n=84)	PATIENTS WITHOUT CLC (n=101)
Number of prior ASMs[a], n (%)		
0-1	18 (21.4)	32 (31.7)
2-4	36 (42.9)	53 (52.5)
≥5	30 (35.7)	16 (15.8)
Number of concomitant ASMs[b], mean (SD)	3.6 (2.1)	3.1 (2.1)
Concomitant ASMs[b] taken by ≥20% of patients in either subgroup, n (%)		
Valproate	32 (38.1)	47 (46.5)
Diazepam	28 (33.3)	22 (21.8)
Lamotrigine	26 (31.0)	17 (16.8)
Lacosamide	24 (28.6)	10 (9.9)
Clobazam	22 (26.2)	26 (25.7)
Oxcarbazepine	21 (25.0)	24 (23.8)
Phenytoin	21 (25.0)	24 (23.8)
Topiramate	20 (23.8)	28 (27.7)
Carbamazepine	17 (20.2)	34 (33.7)

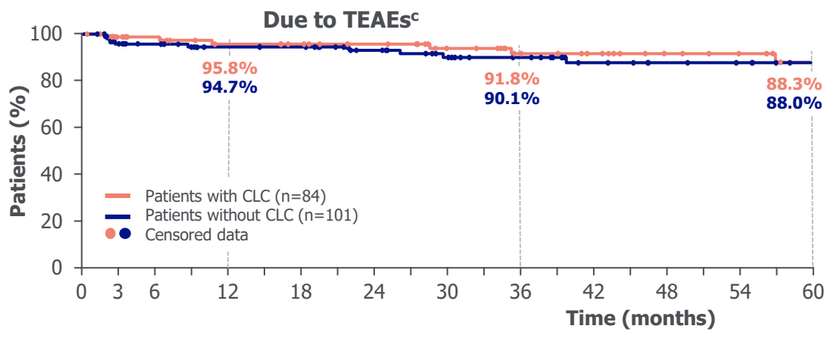
[a]For directly enrolled patients, prior ASMs include any medications that started prior to the first dose of trial drug in N01266 and with stop dates before the date of first dose in N01266; for long-term follow-up patients, prior ASMs include any medications that started and stopped prior to the first dose in the core trial; [b]Concomitant ASMs include any medications that were taken for ≥1 day during the trial period. ASM, antiseizure medication; CLC, cognitive or learning comorbidities.

RETENTION

Kaplan-Meier estimates for time to BRV discontinuation[a] (SS)







[a]One month was defined as 30 days; [b]Patients who discontinued for reasons other than lack of efficacy were censored; [c]Patients who discontinued for reasons other than TEAEs were censored. CLC, cognitive or learning comorbidities; TEAE, treatment-emergent adverse event.

- Generally, no differences were observed between patients with vs without CLC in the estimated proportion of BRV discontinuations due to any reason, due to lack of efficacy, or due to TEAEs.

EFFICACY

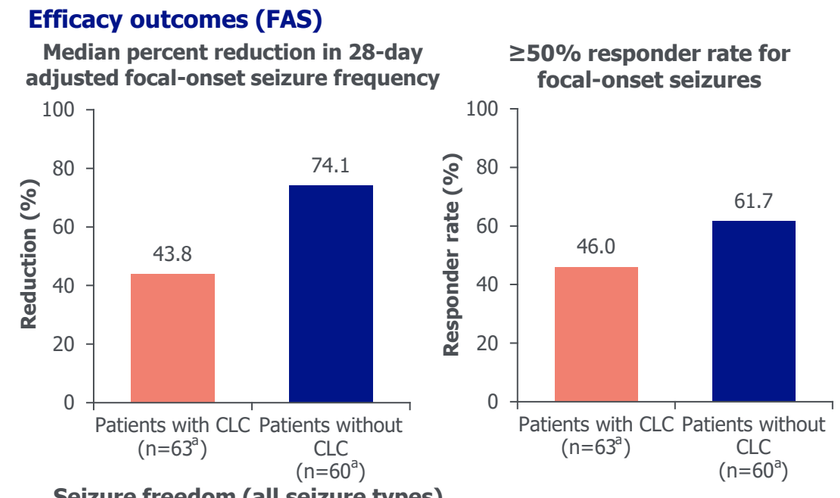
- 166 patients were >2 years of age and included in the efficacy analyses (FAS).

Baseline seizure frequency (FAS)

	PATIENTS WITH CLC (n=78)	PATIENTS WITHOUT CLC (n=88)
Baseline focal-onset seizure frequency per 28 days, median	11.3	8.7

CLC, cognitive or learning comorbidities.

Efficacy outcomes (FAS)

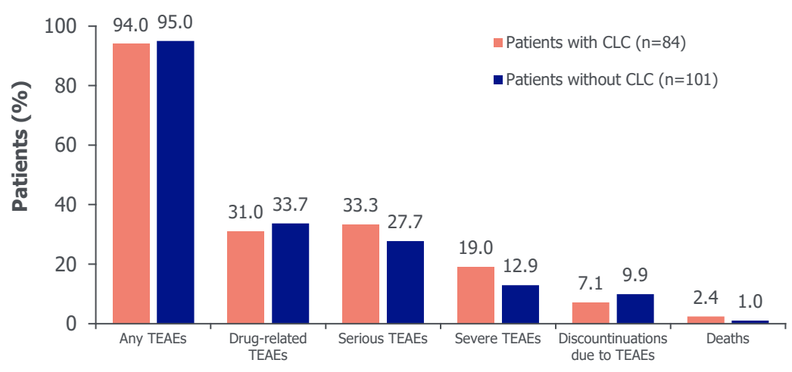


[a]Number of patients with available data; [b]At any time during the evaluation period; [c]Patients with ≥12 months of treatment. CLC, cognitive or learning comorbidities

- In patients >2 years of age with vs without CLC, efficacy assessments showed numerically lower but still clinically relevant:
  - Median percent reduction from baseline in 28-day adjusted focal-onset seizure frequency
  - 50% responder rates for focal-onset seizures
  - ≥12-month continuous seizure freedom from all seizure types (in patients with at least 12 months of treatment).

SAFETY AND TOLERABILITY

Overview of treatment-emergent adverse events (SS)



CLC, cognitive or learning comorbidities; TEAE, treatment-emergent adverse event.

Treatment-emergent adverse events (SS)

PATIENTS, n (%)	PATIENTS WITH CLC (n=84)	PATIENTS WITHOUT CLC (n=101)
TEAEs[a] reported by ≥20% of patients in either subgroup		
Pyrexia	28 (33.3)	14 (13.9)
Nasopharyngitis	25 (29.8)	27 (26.7)
Vomiting	18 (21.4)	19 (18.8)
Pharyngitis	17 (20.2)	29 (28.7)
Seizure	13 (15.5)	21 (20.8)
Pharyngotonsillitis	10 (11.9)	21 (20.8)
Headache	9 (10.7)	22 (21.8)
Drug-related TEAEs[a] reported by ≥3 patients in either subgroup		
Somnolence	6 (7.1)	3 (3.0)
Decreased appetite	6 (7.1)	2 (2.0)
Fatigue	4 (4.8)	2 (2.0)
Aggression	3 (3.6)	2 (2.0)
Seizure	2 (2.4)	3 (3.0)
Abnormal behavior	0	3 (3.0)
TEAEs[a] leading to discontinuation in ≥2 patients in either subgroup		
Status epilepticus	0	2 (2.0)
Suicidal ideation	0	3 (3.0)

[a]Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 Preferred Term. CLC, cognitive or learning comorbidities; TEAE, treatment-emergent adverse event..

Conclusions

- In this analysis, pediatric patients with focal-onset seizures and ongoing CLC were generally more difficult to treat than those without CLC.
- No differences were observed between patients with vs without CLC in the estimated proportion of BRV discontinuations due to any reason, due to lack of efficacy, or due to TEAEs.
- Although the observed efficacy response was numerically lower in patients with vs without CLC, it still indicated a clinically relevant seizure frequency reduction.
- The incidences of TEAEs, drug-related TEAEs, serious TEAEs, and discontinuations due to TEAEs during long-term BRV treatment were similar in patients with and without CLC.
- This analysis indicated that BRV was a well tolerated and efficacious antiseizure medication for both difficult-to-treat pediatric patients with CLC and those without CLC.

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