Long-Term Tolerability and Efficacy of Adjunctive Brivaracetam in Pediatric Patients With Primary Generalized Seizures: Subgroup Analysis of an Open-Label, Follow-Up Trial

Lieven Lagae[1]
Christine de la Loge[2]
Sami Elmoufti[3]
Jan-Peer Elshoff[4]
Brian Moseley[3]
Kristy Pucylowski[5]
Dimitrios Bourikas[6]

1. Department of Development and Regeneration, Pediatric Neurology Section, University Hospitals Leuven, Leuven, Belgium
2. UCB Pharma, Brussels, Belgium
3. UCB Pharma, Morrisville, NC, USA
4. UCB Pharma, Monheim am Rhein, Germany
5. UCB Pharma, Smyrna, GA, USA
6. UCB Pharma, Alimos, Greece

Background

- Only a limited number of antiseizure medications (ASMs) are approved for treatment of patients with primary generalized seizures (PGS), particularly for treatment of young children.[1,2]
  - Patients with PGS can demonstrate cognitive impairment or behavioral issues.[3-5]
  - Further, some ASMs have been associated with negative outcomes on cognition[6] or behavior.[7]
- Brivaracetam (BRV) is indicated for the treatment of focal-onset (partial-onset) seizures in patients ≥1 month of age in the United States,[8] and as adjunctive therapy for the treatment of focal-onset seizures in patients ≥2 years of age with epilepsy in the European Union.[9]
- A recent Phase III trial evaluated long-term safety, tolerability, and efficacy of adjunctive BRV in pediatric patients with epilepsy for up to 9.5 years of exposure.[10]

Objective

- To evaluate long-term safety, tolerability, and efficacy of adjunctive BRV in a subgroup of pediatric patients with PGS at baseline, as well as changes to behavior and emotional function.

Methods

TRIAL DESIGN

- N01266 (ClinicalTrials.gov: NCT01364597) was a Phase III, open-label, single-arm, multicenter trial that evaluated the long-term safety, tolerability, and efficacy of BRV as adjunctive treatment in children with epilepsy.[10]
  - Patients who enrolled from a core BRV trial (ie, long-term follow-up patients from N01263 [NCT00422422], EP0065 [NCT03405714], or N01349 [NCT03325439]) must have been ≥1 month to <16 years of age upon entry into the core trial (N01263 and EP0065) or term/preterm neonates ≤27 days of postnatal age (N01349); eligible patients who enrolled in N01266 without having participated in a core trial (ie, direct enrollers) must have been ≥4 to <17 years of age (all of these had focal-onset seizures).
  - Patients received a maximum of 5 mg/kg/day BRV as tablet or oral solution (maximum ≤200 mg/day).

ANALYSIS

- Subgroup analysis of patients with PGS[a] at baseline.
- Safety Set (SS): all patients who enrolled and took ≥1 dose of BRV in this trial.
- Full Analysis Set (FAS): all patients in the SS who had ≥1 completed post-baseline daily record card (documenting seizure occurrence).
- Assessed outcomes: BRV treatment retention, tolerability (incidence of treatment-emergent adverse events [TEAEs]), efficacy (median percent reduction in 28-day adjusted total seizure frequency from baseline[b] to the end of the evaluation period, ≥50% responder rate for all seizures [responders were defined as having ≥50% reduction in seizure frequency compared with baseline], and seizure freedom from all seizures during the entire evaluation period), behavior and emotional function (mean changes from baseline to last evaluation in Achenbach Child Behavior Checklist [CBCL] 1.5-5/CBCL 6-18 raw syndrome scores and shift in T-score categories).
  - Pre-specified seizure-related outcomes were assessed for subgroups of patients <2 and ≥2 years of age (at core trial entry) using daily record card data.
  - Kaplan-Meier–estimated retention on BRV and change in Achenbach CBCL scores were assessed post hoc.
  - T-score categories for Achenbach CBCL were classified as 'normal' (<65) or 'borderline or clinical range (BCR)' (≥65).

[a]Defined as patients with typical absence, atypical absence, myoclonic, clonic, tonic, tonic-clonic, and/or atonic seizures entered on ILAE Seizure Classification History eCRF page at screening, or reported on the Historical Seizure Count eCRF page for the last 3 weeks before screening with a nonzero value; [b]Baseline values from core trials were used as baseline if available, otherwise the most recent available measurement between day of final measurement in the core trial and day before first BRV administration in N01266 was used. eCRF, electronic case report form.

Results

BASELINE DEMOGRAPHICS

- Of 257 patients receiving BRV in this trial (SS), 68 (26.5%) patients had PGS.
- 14 (20.6%) and 54 (79.4%) patients with PGS were <2 and ≥2 years of age, respectively.

Baseline demographics and epilepsy characteristics (SS)

	PATIENTS WITH PGS (N=68)
Age, mean (SD), years	6.7 (4.6)
Male, n (%)	34 (50.0)
Weight, mean (SD), kg	25.3 (19.3)
Epilepsy duration, mean (SD), years	3.9 (3.4)
Age at diagnosis, mean (SD), years	2.8 (3.4)
Number of prior ASMs[a], median (range)	3.0 (0, 12)
0-1, n (%)	24 (35.3)
2-4, n (%)	24 (35.3)
≥5, n (%)	20 (29.4)
Prior and ongoing medical conditions[b,c] reported by ≥20% of patients, n (%)	
Any medical conditions	63 (92.6)
Nervous system disorders	38 (55.9)
Congenital, familial, and genetic disorders	28 (41.2)
Infections and infestations	22 (32.4)
Psychiatric disorders	21 (30.9)
Gastrointestinal disorders	16 (23.5)
Respiratory, thoracic, and mediastinal disorders	14 (20.6)

Patients with PGS had a wide range of epileptic syndromes reported on eCRF (genetic testing was not commonplace when the core trials started enrollment). [a]Any ASMs that started prior to first dose of trial drug and with stop dates before date of first dose in N01266 (direct enrollers), or any ASMs that started and stopped prior to first dose in core trial (long-term follow-up patients); [b]Included both resolved and ongoing medical conditions at day of first BRV dose in core trials (long-term follow-up patients) or at day of first BRV dose in N01266 (direct enrollers); [c]Medical Dictionary for Regulatory Activities Version 18.1 System Organ Class. ASM, antiseizure medication; PGS, primary generalized seizures. eCRF, electronic case report form.

Overview

QUESTION

What are the long-term retention, tolerability, and efficacy of adjunctive brivaracetam (BRV) in pediatric patients with primary generalized seizures (PGS)?

INVESTIGATION

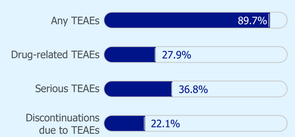
Pre-specified and post hoc analyses of a Phase III, open-label, follow-up trial (N01266, NCT01364597). Subgroup analyses were performed for patients with PGS at baseline (N=68).

RESULTS

Kaplan-Meier–estimated BRV treatment retention (N=68)

1 year 61.8%
3 years 47.7%
5 years 43.3%

Tolerability (N=68)

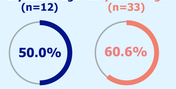


TEAE, treatment-emergent adverse event.

Efficacy

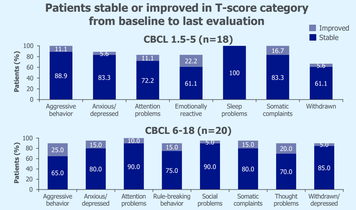
Median percent reduction in 28-day adjusted total seizure frequency

≥50% responder rate for all seizures



Achenbach CBCL

Patients stable or improved in T-score category from baseline to last evaluation



CBCL, Child Behavior Checklist.

CONCLUSIONS

In this subgroup analysis of a Phase III trial, long-term adjunctive BRV was well tolerated and efficacious in pediatric patients ≥1 month of age with PGS.
During long-term adjunctive BRV treatment, behavior and emotional function were generally stable in patients 1.5-5 years of age and slightly improved in patients 6-18 years of age.

For a copy of the poster scan or visit: UCBposters.com/AES2024
Poster ID: AES2024-2.362

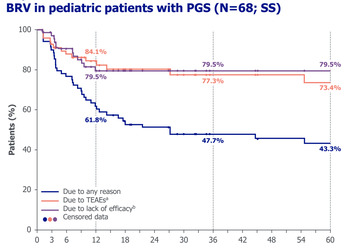
PATIENT DISPOSITION

- Overall, 28 (41.2%) patients with PGS completed the trial and 40 (58.8%) discontinued the trial.
  - The most common primary reasons for discontinuation (≥10% of patients) were adverse event (22.1%), lack of efficacy (17.6%), and withdrawn consent (11.8%).

EXPOSURE AND RETENTION ON BRV

- Median modal BRV dose was 3.63 mg/kg/day.

Kaplan-Meier estimates for time to discontinuation of BRV in pediatric patients with PGS (N=68; SS)

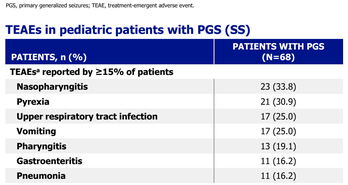


One month was defined as 30 days. Patients completing the trial were censored at the end of BRV treatment. [a]Patients who discontinued for reasons other than TEAEs were censored; [b]Patients who discontinued for reasons other than lack of efficacy were censored. PGS, primary generalized seizures; TEAE, treatment-emergent adverse event.

- Kaplan-Meier–estimated retention on BRV at 12, 36, and 60 months was 61.8%, 47.7%, and 43.3%, respectively.
- Similar proportions of patients discontinued due to TEAEs or lack of efficacy.

SAFETY AND TOLERABILITY

Overview of TEAEs in pediatric patients with PGS (N=68; SS)



PGS, primary generalized seizures; TEAE, treatment-emergent adverse event.

TEAEs in pediatric patients with PGS (SS)

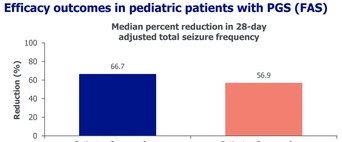
PATIENTS, n (%)	PATIENTS WITH PGS (N=68)
TEAEs[a] reported by ≥15% of patients	
Nasopharyngitis	23 (33.8)
Pyrexia	21 (30.9)
Upper respiratory tract infection	17 (25.0)
Vomiting	17 (25.0)
Pharyngitis	13 (19.1)
Gastroenteritis	11 (16.2)
Pneumonia	11 (16.2)
Drug-related TEAEs[a] reported by ≥3 patients	
Aggression	5 (7.4)
Decreased appetite	3 (4.4)
Fatigue	3 (4.4)
Somnolence	3 (4.4)

[a]Medical Dictionary for Regulatory Activities Version 18.1 Preferred Term. PGS, primary generalized seizures; TEAE, treatment-emergent adverse event.

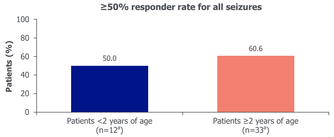
EFFICACY

Efficacy outcomes in pediatric patients with PGS (FAS)

Median percent reduction in 28-day adjusted total seizure frequency



≥50% responder rate for all seizures

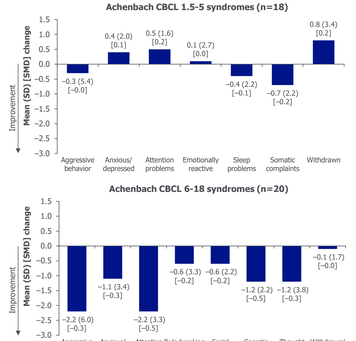


Seizure freedom (all seizure types)[b]

[a]Number of patients with available data; [b]During the entire evaluation period. PGS, primary generalized seizures.

ACHENBACH CBCL

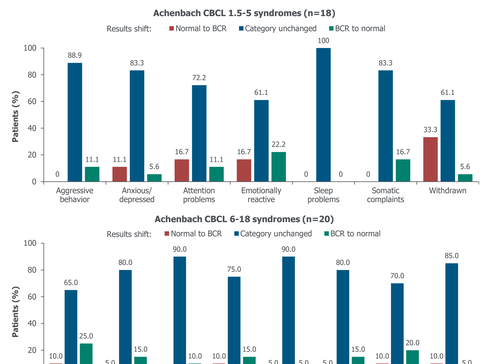
Change in Achenbach CBCL syndromes scores from baseline to last evaluation in patients with PGS (SS)



Only includes patients with baseline and ≥1 post-baseline result. Baseline data were obtained from the core trial screening visit. Median time to last evaluation was 6.9 months for CBCL 1.5-5 (n=18) and 9.3 months for CBCL 6-18 (n=20). CBCL, Child Behavior Checklist; PGS, primary generalized seizures; SMD, standardized mean difference.

- Mean changes from baseline to last evaluation in Achenbach CBCL 1.5-5 raw syndrome scores fluctuated around 0 and were of minimal or small amplitude.
- Mean changes from baseline to last evaluation in Achenbach CBCL 6-18 raw syndrome scores showed small improvements for most syndromes.

Shift in T-score categories in Achenbach CBCL syndromes from baseline to last evaluation in patients with PGS (SS)



Only patients providing data at both baseline and last evaluation were included. Baseline data were obtained from the core trial screening visit. Findings are based on T-scores (normal <65; BCR ≥65). BCR, borderline or clinical range; CBCL, Child Behavior Checklist; PGS, primary generalized seizures.

- At last evaluation, most patients remained in their baseline T-score category for each syndrome (range: 61.1-100%).

Limitations

- Subgroup analysis of open-label trial.
- Interpretation of some outcomes is limited by the small sample size.
- Patient numbers were too low to perform separate analyses for patients with specific seizure types.

Conclusions

- In this subgroup analysis of a Phase III trial, long-term adjunctive BRV was well tolerated and efficacious in pediatric patients ≥1 month of age with PGS.
- During long-term adjunctive BRV treatment, behavior and emotional function were generally stable in patients 1.5-5 years of age and slightly improved in patients 6-18 years of age.
- Long-term use of BRV in children with PGS is an efficacious and well-tolerated option that does not appear to adversely affect behavior and emotional functioning.

References

1. Fonseca E, et al. *Epilepsy Behav* 2020;102:106657.
2. Vina-Rehl N, et al. *Epilepsy Behav* 2020;107:107067.
3. Ratcliffe C, et al. *Front Neurol* 2020;11:144.
4. Caplan R, et al. *Epilepsia* 2008;49(11):1838-1846.
5. Taura M, et al. *Epilepsy Behav* 2020;105:106958.
6. Park S-P and Kwon S-H. *J Clin Neurol* 2008;4(3):99-106.
7. Eddy CM, et al. *J Clin Psychopharmacol* 2012;32(3):362-375.
8. Briviact® (brivaracetam) US Prescribing Information. UCB Inc. 2023. www.briviact.com/briviact-PI.pdf Accessed September 16, 2024.
9. Briviact® (brivaracetam) EU Summary of Product Characteristics. UCB Pharma SA. 2024. www.ema.europa.eu/en/documents/product-information/briviact-epar-product-information_en.pdf Accessed September 16, 2024.
10. Lagae L, et al. *Epilepsia* 2023;64(11):2934-2946.

UCB Pharma-sponsored. UCB Pharma was involved in the design of the study, the collection, analysis, and interpretation of data, and review of the poster. The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to this trial. The authors acknowledge Bobby Jacob, PharmD (UCB Pharma, Smyrna, GA, USA) for managing the development of the poster, and Michaela Fuchs, PhD (Evidence Scientific Solutions Ltd., Horsham, UK) for writing assistance, which was funded by UCB Pharma. Author contributions: C de la Loge, S Elmoufti, J-P Elshoff, B Moseley, K Pucylowski, and D Bourikas designed the study. All authors analyzed and interpreted the data. All authors critically reviewed the poster and approved the final version for presentation. Author disclosures: L Lagae received grants and is a consultant and/or speaker for Eisai, Epihunter, GW Pharma, LivaNova, Novartis, Shire, Takeda/Ovid, and UCB Pharma. C de la Loge is contracted by UCB Pharma. S Elmoufti, J-P Elshoff, B Moseley, K Pucylowski, and D Bourikas are employees of UCB Pharma and have received stocks from their employment.

For a copy of this poster, use your smartphone to scan the QR code, download from the website below, visit the UCB medical affairs booth at the exhibit, or contact UCBCares®
Website: UCBposters.com/AES2024; Poster ID: **AES2024-2.362**
Phone: +1-844-599-CARE (2273)
Email: UCBCares@ucb.com

American Epilepsy Society 78th Annual Meeting
Los Angeles, CA, USA | December 6–10, 2024