Tolerability and Efficacy of Adjunctive Brivaracetam in Japanese and Chinese Patients With Focal-Onset Seizures: Interim and Post Hoc Analysis of a Phase 3, Open-Label Extension Trial

Ayataka Fujimoto[1]
Bing Qin[2]
Dong Zhou[3]
Dimitrios Bourikas[4]
Najla Dickson[5]
Brian Moseley[5]
Tomonobu Sano[6]
Tadaharu Soma[6]
Weiwei Sun[7]
Jun Watanabe[6]
Yushi Inoue[8]

1. Seirei Hamamatsu General Hospital, Shizuoka, Japan
2. The First Affiliated Hospital of Jinan University, Guangdong, China
3. West China Hospital of Sichuan University, Sichuan, China
4. UCB Pharma, Alimos, Greeece
5. UCB Pharma, Morrisville, NC, USA
6. UCB Pharma, Tokyo, Japan
7. UCB Pharma, Shanghai, China
8. National Epilepsy Center, National Hospital Organization Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

Background

- Brivaracetam (BRV) is an antiseizure medication (ASM) with high and selective affinity for synaptic vesicle protein 2A in the brain.[1,2]
- BRV was recently approved in Japan as monotherapy and adjunctive therapy for the treatment of focal-onset seizures with or without secondary generalization in adult patients aged ≥15 years with epilepsy.[3,4]
- It is important that the efficacy, tolerability, and safety of ASMs are maintained over the long term, given that chronic treatment is required by many patients with epilepsy.

Objective

- To evaluate the long-term safety, tolerability, and maintenance of efficacy of adjunctive BRV in Japanese and Chinese patients aged ≥16 years with focal-onset seizures.

Methods

TRIAL DESIGN

- This was an interim and post hoc analysis of data from EP0085 (ClinicalTrials.gov: NCT03250377),[5] an ongoing, open-label, long-term follow-up trial of adjunctive BRV 50-200 mg/day in Japanese and Chinese patients aged ≥16 years with focal-onset seizures after all patients had the opportunity to complete ≥48 weeks in the trial.
- The trial population includes patients who rolled over from 2 previous BRV studies (EP0083 [NCT03083665][6] and N01379 [NCT01339559][7]) and directly enrolled patients.
  - For patients who rolled over into EP0085, baseline was the baseline period of the core trial (EP0083 or N01358/NCT01261325 [the core trial of N01379]).
  - For direct enrollers, the baseline period for seizure outcomes was the 8 weeks before first BRV administration; for all other outcomes, the baseline period was trial days on or after the EP0085 screening visit and before the start of the evaluation period in EP0085.
- Rollover patients from N01379 were started at a dose of up to 200 mg/day BRV.
- Directly enrolled patients and rollover patients from EP0083 were started on BRV 100 mg/day (50 mg twice daily) and maintained at this dose for at least 2 weeks unless they were unable to tolerate this treatment.
- The dose of BRV could be adjusted between 50 mg/day and 200 mg/day, according to seizure control and tolerability.

ANALYSES

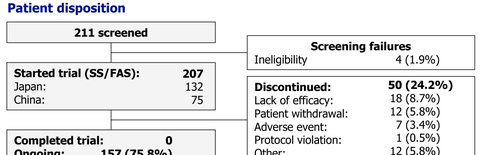
- The Safety Set (SS) includes all enrolled patients who took ≥1 dose of BRV in EP0085.
- The Full Analysis Set (FAS) includes all patients in the SS with ≥1 seizure record on the daily record card during the evaluation period (patients could have recorded 0 seizures).
- The primary safety outcome is the incidence of treatment-emergent adverse events (TEAEs).
- Post hoc analyses included the change in number of concomitant ASMs and BRV daily dose during the initial 12 months in the trial, and the Kaplan-Meier–estimated proportion of patients not discontinuing BRV due to any reason, due to lack of efficacy, due to TEAEs, or due to lack of efficacy or TEAEs over time.

Results

PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

- The first patient was enrolled on August 5, 2017.
- At data cutoff (June 1, 2023), 207 patients had enrolled and had the opportunity to complete ≥48 weeks in the trial (132 [63.8%] in Japan, and 75 [36.2%] in China).
- All 207 patients were included in both the SS and FAS.

Patient disposition



Overview

QUESTION

What are the long-term safety, tolerability, and maintenance of efficacy of adjunctive brivaracetam (BRV) in Japanese and Chinese patients aged ≥16 years with focal-onset seizures?

INVESTIGATION

Interim and post hoc analysis of data from EP0085 (NCT03250377), an ongoing, open-label, long-term follow-up trial of adjunctive BRV 50-200 mg/day in Japanese and Chinese patients after all patients had the opportunity to complete ≥48 weeks in the trial (N=207 at data cutoff on June 1, 2023).

RESULTS

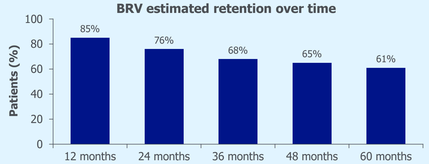
Duration of BRV exposure

Mean: 667.8 days

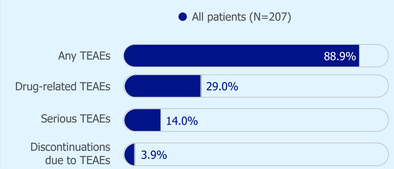
Median: 427.0 days

Estimated retention (N=207)

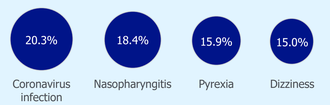
BRV estimated retention over time



Tolerability



Most common TEAEs (occurring in ≥15% of all patients)



TEAE, treatment-emergent adverse event.

CONCLUSIONS

Estimated BRV retention at 1, 3, and 5 years was 85%, 68%, and 61%, respectively. Over 5 years of treatment, the estimated proportion of patients discontinuing due to treatment-emergent adverse events was low (≤5%). Based on this interim and post hoc analysis, long-term adjunctive BRV was well tolerated and efficacious in Japanese and Chinese patients with focal-onset seizures.

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Baseline demographics and epilepsy characteristics

	ALL PATIENTS (N=207)
Age, mean (SD), years	36.7 (14.1)
Female, n (%)	107 (51.7)
Ethnic subgroup, n (%)	
Japanese	131 (63.3)
Chinese	75 (36.2)
Other	1 (0.5)
Age at onset of epilepsy, mean (SD), years	19.50 (15.26)[a]
Duration of epilepsy, mean (SD), years	17.16 (13.10)[a]
Baseline focal-onset seizure frequency/28 days, median (Q1, Q3)	7.59 (4.39, 20.00)
Seizure classification at any time before core trial entry[b], n (%)	
Any focal seizures *(partial onset)*	207 (100.0)
Focal aware *(simple partial)*	104 (50.2)
Focal impaired awareness *(complex partial)*	174 (84.1)
Focal to bilateral tonic-clonic *(partial evolving to secondarily generalized)*	110 (53.1)
Any generalized-onset seizures	6 (2.9)
Tonic	3 (1.4)
Tonic-clonic	4 (1.9)
Unclassified epileptic seizures	2 (1.0)
Number of previous ASMs[c], n (%)	
0-1	78 (37.7)
2-4	74 (35.7)
≥5	55 (26.6)

[a]n=206; [b]Patients could have had >1 response. Seizure types are listed per the ILAE 2017 classification[8] with the seizure types per the trial protocol (ILAE 1981)[9] provided in parentheses; [c]Previous ASMs are ASMs taken at any time and discontinued before entry into the previous double-blind trial for rollover patients or before entry into EP0085 for direct enrollers.
ASM, antiseizure medication; ILAE, International League Against Epilepsy; Q1, 25th percentile; Q3, 75th percentile.

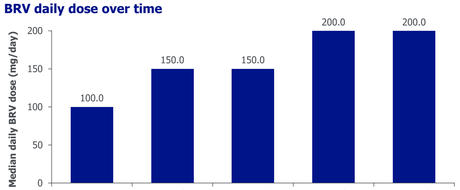
CONCOMITANT ASMs

- The most common concomitant ASMs taken at least once during treatment with BRV (in ≥25% of all patients) were lacosamide (73 [35.3%]), carbamazepine (67 [32.4%]), valproate (62 [30.0%]), and lamotrigine (61 [29.5%]).
- Overall, the median number of concomitant ASMs from trial entry through 12 months of treatment was 2.0 (range: 1-7).

BRV EXPOSURE AND DOSING

- At data cutoff, the total duration of BRV exposure was 378.5 patient-years.
- Overall, the mean duration of BRV exposure was 667.8 days (SD: 492.1 days; median: 427.0 days; range: 5-2021 days).
- The median modal dose of BRV was 200.0 mg/day (range: 25.0-200.0 mg/day).

BRV daily dose over time

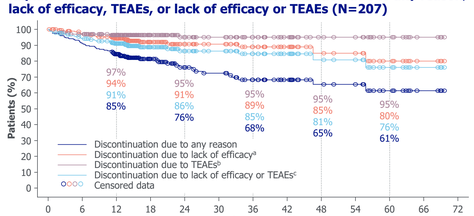


Daily doses for patients who were on BRV at the specified time point based on their duration of exposure to BRV. BRV dose at EP0085 entry is taken from day 2 where full prescribed BRV daily dose is considered to be taken as 2 separate doses (1 in the morning and 1 in the evening). One month was defined as 30 days.

- The median daily dose of BRV was 100.0 mg/day at EP0085 trial entry, which increased and reached a median of 200.0 mg/day after 9 months of treatment.

ESTIMATED BRV RETENTION

Kaplan-Meier–estimated time to BRV discontinuation due to any reason, lack of efficacy, TEAEs, or lack of efficacy or TEAEs (N=207)



TIME (MONTHS)	0	12	24	36	48	60
Number of patients at risk	207	165[d]	64	44	22	11
Cumulative number of events						
Discontinuation of BRV due to any reason	0	32	42	48	49	50
Discontinuation of BRV due to lack of efficacy	0	11	15	16	17	18
Discontinuation of BRV due to TEAEs	0	7	8	8	8	8
Discontinuation of BRV due to lack of efficacy or TEAEs	0	18	23	24	25	26

One month was defined as 30 days. Patients ongoing in the trial are censored at the cutoff date. [a]Patients who discontinued for reasons other than lack of efficacy were censored; [b]Patients who discontinued for reasons other than TEAEs were censored; [c]Patients who discontinued for reasons other than lack of efficacy or TEAEs were censored; [d]n=166 for discontinuation of BRV due to lack of efficacy. TEAE, treatment-emergent adverse event.

- Estimated BRV retention at 1, 2, 3, 4, and 5 years was 85%, 76%, 68%, 65%, and 61%, respectively.
- The Kaplan-Meier–estimated proportion of patients discontinuing due to TEAEs was low over 5 years of treatment (≤5%).
- Most of the discontinuations due to TEAEs were during the first 12 months of treatment.

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SAFETY AND TOLERABILITY

Overall incidence of TEAEs[a]

PATIENTS, n (%)	ALL PATIENTS (N=207)
Any TEAEs	184 (88.9)
Drug-related TEAEs	60 (29.0)
Serious TEAEs[b]	29 (14.0)
Severe TEAEs[c]	8 (3.9)
Discontinuation due to TEAEs	8 (3.9)
TEAEs[d] occurring in ≥10% of all patients	
Coronavirus infection	42 (20.3)
Nasopharyngitis	38 (18.4)
Pyrexia	33 (15.9)
Dizziness	31 (15.0)
Somnolence	27 (13.0)
Upper respiratory tract infection	26 (12.6)
Headache	24 (11.6)
Drug-related TEAEs[c] occurring in ≥5 patients	
Somnolence	19 (9.2)
Dizziness	10 (4.8)
Irritability	5 (2.4)

[a]In all patients who had the opportunity to complete ≥48 weeks in the trial; [b]TEAEs were classified as serious if they met ≥1 of the following criteria: death, life-threatening, significant or persistent disability or incapacity, congenital anomaly or birth defect (including that occurring in a fetus), important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other serious TEAEs, or initial inpatient hospitalization or prolongation of hospitalization (except for hospitalizations for reasons not associated with the occurrence of an adverse event); [c]Severe TEAEs were classified as events that prevented normal everyday activities; [d]Preferred term (Medical Dictionary for Regulatory Activities version 18.1). TEAE, treatment-emergent adverse event.

- Most TEAEs were mild (117 [56.5%]) or moderate (59 [28.5%]) in intensity.
- TEAEs leading to discontinuation were irritability, seizure, and somnolence in 2 (1.0%) patients each, and diarrhea, stomatitis, gait disturbance, malaise, cerebral infarction, epilepsy, and affect lability in 1 (0.5%) patient each.

EFFICACY

- Median focal-onset seizure frequency per 28 days decreased from 7.59 (interquartile range: 4.39, 20.00) during baseline to 4.11 (1.56, 11.79) during the evaluation period.

Conclusions

- Estimated BRV retention at 1, 3, and 5 years was 85%, 68%, and 61%, respectively (165, 44, and 11 patients at risk at each time point, respectively).
- Over 5 years of treatment, the estimated proportion of patients discontinuing due to TEAEs was low (≤5%).
- The median number of concomitant ASMs remained stable through 12 months of treatment, and the median daily BRV dose increased to the maximum recommended dose of 200 mg/day after 9 months of treatment.
- Based on this interim and post hoc analysis, long-term adjunctive BRV was well tolerated and efficacious in Japanese and Chinese patients with focal-onset seizures.

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