Time Course of Treatment-Emergent Adverse Events in Adult Asian Patients With Focal-Onset Seizures During Adjunctive Brivaracetam Treatment: A Post Hoc Analysis of a Phase III, Randomized Trial

Naotaka Usui[1]
Dong Zhou[2]
Bin Qin[3]
Somsak Tiamkao[4]
Leonor Cabral-Lim[5]
Kheng Seang Lim[6]
Shih-Hui Lim[7]
Jing-Jane Tsai[8]
Jun Watanabe[9]
Weiwei Sun[10]
Najla Dickson[11]
Dimitrios Bourikas[12]
Brian Moseley[11]
Yushi Inoue[13]

1. NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka
2. West China Hospital of Sichuan University, Sichuan
3. The First Affiliated Hospital of Jinan University, Guangdong
4. Khon Kaen University, Srinagarind Hospital, Khon Kaen
5. Department of Neurosciences, College of Medicine, Philippine General Hospital, University of the Philippines Manila, The Health Sciences Center, Manila
6. Division of Neurology, Department of Medicine, Universiti Malaya, Kuala Lumpur
7. Singapore General Hospital
8. Department of Neurology, National Cheng Kung University Hospital, Tainan
9. UCB Pharma, Tokyo
10. UCB Pharma, Shanghai
11. UCB Pharma, Morrisville, NC
12. UCB Pharma, Alimos
13. NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka

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Background

- Brivaracetam (BRV) is indicated for mono- and adjunctive therapy for focal-onset (partial-onset) seizures (FOS) in patients ≥1 month of age in the United States, and for adjunctive therapy in patients ≥2 years of age in the European Union.[1,2]
- In Japan, BRV was recently approved for mono- and adjunctive therapy for FOS with or without secondary generalization in adult patients (aged ≥15 years).[3,4]
- In the Asia-Pacific region, BRV is approved in the Province of Taiwan for mono-and adjunctive therapy for FOS in patients aged ≥4 years (intravenous formulation approved in adults ≥16 years). BRV is not available in Thailand, China Mainland, the Philippines, Malaysia, or Singapore.
- A Phase III clinical trial (EP0083) found adjunctive BRV to be efficacious and well tolerated in Asian patients with FOS.[5]
  - Somnolence and dizziness were the most common treatment-emergent adverse events (TEAEs); in all patients on BRV, somnolence and dizziness were reported in 14.4% and 12.7% of patients, respectively.
- In clinical trials, TEAEs are usually reported for the full treatment period.
- To guide clinician monitoring and patient expectations, it is beneficial to know the time course of TEAE occurrence.
- Evidence suggests most drug-related central nervous system TEAEs occur early in the course of BRV treatment, before habituating over several weeks.[6]

Objective

- To assess the time course of TEAEs overall and the most frequently reported TEAEs in adult Asian patients with FOS during adjunctive BRV treatment.

Methods

TRIAL DESIGN

- EP0083 (NCT03083665) was a Phase III, randomized, double-blind, placebo-controlled trial evaluating BRV 50 mg/day and 200 mg/day in adult Asian patients with FOS with or without secondary generalization despite current treatment with 1 or 2 concomitant antiseizure medications (ASMs).
  - Patients (≥16-80 years of age) were selected from 94 participating sites located in Thailand, Japan, China Mainland, the Philippines, Malaysia, Singapore, and the Province of Taiwan.
- The total duration of the trial was 26 weeks (maximum 16 weeks of exposure to BRV), comprising an 8-week prospective baseline period, a 12-week treatment period, followed by a 4-week down-titration period and 2-week trial drug-free period or 2-week transition period (for patients continuing treatment in an open-label extension trial [EP0085] or managed access program).
- Following the 8-week baseline period, patients were randomized to 3 treatment arms in a 1:1:1 ratio (placebo; BRV 50 mg/day; BRV 200 mg/day) and entered the double-blind treatment period.

POST HOC ANALYSIS

- Performed on the Safety Set (SS): all randomized patients who received ≥1 dose of trial medication.
- The most frequently reported drug-related TEAEs were defined as those reported in ≥5% of all patients on BRV during the 12-week treatment period (in this post hoc analysis, this included only drug-related somnolence and dizziness).
- Assessments included:
  - TEAEs: intensity, incidence, and prevalence.
  - Discontinuation due to TEAEs.
  - Drug-related TEAEs: intensity, incidence, and prevalence.
  - Drug-related somnolence and dizziness: intensity, incidence, prevalence, time to onset, incidence by number of concomitant ASMs, and resolution status.

Results

PATIENT DISPOSITION, BASELINE DEMOGRAPHICS, AND EXPOSURE[5]

- Of the 449 patients in the Randomized Set (RS), 448 received ≥1 dose of trial medication (placebo, BRV 50 mg/day, BRV 200 mg/day: N=149, 151, and 148, respectively) and were included in the SS.
- The mean (SD) age of patients in the placebo, BRV 50 mg/day, and BRV 200 mg/day groups was 34.5 (13.2), 33.8 (12.6), and 35.2 (13.2) years, respectively (SS).
- In the placebo, BRV 50 mg/day, and BRV 200 mg/day groups, 55.0%, 50.3%, and 56.1%, respectively, were female (SS).
- Overall, 92.6% (n=138/149), 96.7% (n=147/152), and 94.6% (n=140/148) of patients on placebo, BRV 50 mg/day, and BRV 200 mg/day, respectively, completed the trial (RS).
- In all patients exposed to BRV during the treatment period (N=299), the median (range) duration of exposure was 85.0 (1-96) days (SS).

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Overview

QUESTION

What is the time course of treatment-emergent adverse events (TEAEs) in adult Asian patients with focal-onset seizures (FOS) during adjunctive brivaracetam (BRV) treatment?

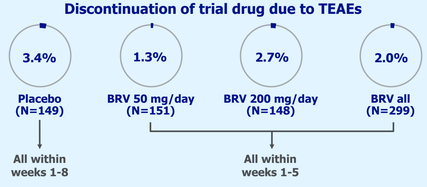
INVESTIGATION

A post hoc analysis of a Phase III, randomized, double-blind, placebo-controlled trial (EP0083; NCT03083665) evaluating BRV 50 mg/day and 200 mg/day in adult patients (≥16-80 years of age) with FOS with or without secondary generalization. The time course of TEAEs, including drug-related somnolence and dizziness, was assessed over the 12-week treatment period.

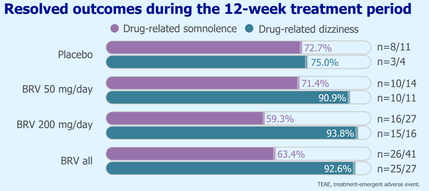
RESULTS

Incidence of drug-related TEAEs by week of treatment

Discontinuation of trial drug due to TEAEs



Resolved outcomes during the 12-week treatment period



TEAE, treatment-emergent adverse event.

CONCLUSIONS

In Asian adults with FOS, the incidence of TEAEs and drug-related TEAEs was highest during the first week of adjunctive BRV treatment and decreased thereafter. Discontinuations due to TEAEs were low and generally occurred during the first 5 weeks of treatment. Most incidences of drug-related somnolence and dizziness were resolved during the 12-week treatment period. These tolerability data could help inform patient monitoring and treatment decisions.

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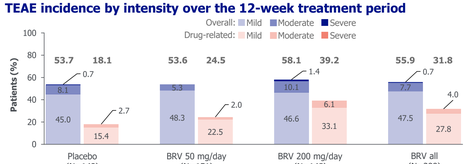
POST HOC ANALYSIS OVER THE 12-WEEK TREATMENT PERIOD (SS)

Epilepsy characteristics

	PLACEBO (N=149)	BRV 50 mg/day (N=151)	BRV 200 mg/day (N=148)	BRV ALL (N=299)
Duration of epilepsy, mean (SD), years	17.03 (11.87)	17.05 (12.20)[a]	15.42 (12.55)	16.24 (12.38)[b]
Age at onset of epilepsy, mean (SD), years	18.01 (14.12)	17.18 (11.78)[a]	20.27 (13.71)	18.71 (12.85)[b]
Baseline FOS frequency/28 days, median (Q1, Q3)	10.00 (5.50, 22.21)	8.98 (5.09, 17.50)	7.82 (5.00, 16.50)	8.15 (5.00, 16.59)
Number of ASMs taken at trial entry,[c] n (%)				
1	67 (45.0)	50 (33.1)	49 (33.1)	99 (33.1)
2	82 (55.0)	101 (66.9)	99 (66.9)	200 (66.9)
≥3	0	0	0	0

[a]n=150; [b]n=298; [c]Only ASMs ongoing at the time of trial entry are summarized. ASM, antiseizure medication; FOS, focal-onset seizure.

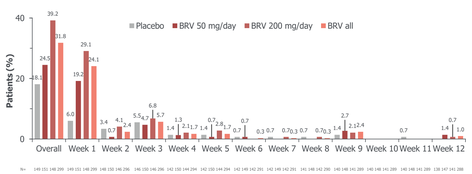
TEAE incidence by intensity over the 12-week treatment period



TEAE, treatment-emergent adverse event.

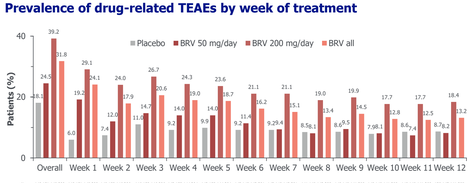
- The overall incidence of TEAEs was similar across treatment arms; drug-related TEAEs was numerically higher in patients on BRV 200 mg/day. Most of the TEAEs were of mild intensity. No severe drug-related TEAEs were reported.
- For patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively, discontinuation of trial drug due to TEAEs was 3.4%, 1.3%, 2.7%, and 2.0% (N=149, 151, 148, 299).
  - Patients only discontinued due to TEAEs during the first 5 weeks of BRV treatment (for placebo, discontinuations due to TEAEs were between weeks 1 and 8).

Incidence of drug-related TEAEs by week of treatment



TEAE, treatment-emergent adverse event.

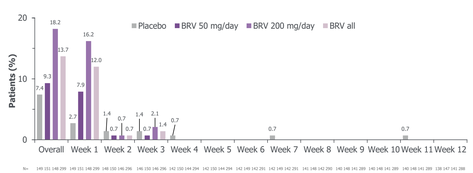
Prevalence of drug-related TEAEs by week of treatment



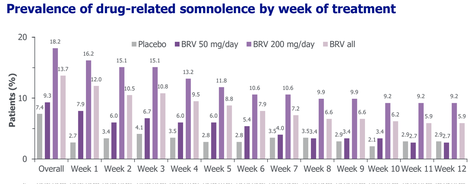
TEAE, treatment-emergent adverse event.

- The incidence of TEAEs and drug-related TEAEs was highest during the first week of adjunctive BRV treatment and decreased thereafter.
- For patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively, incidence of TEAEs was 20.1% (N=149), 31.1% (N=151), 35.8% (N=148), and 33.4% (N=299), respectively, in week 1, and 4.3% (N=138), 6.8% (N=147), 5.0% (N=141), and 5.9% (N=288), respectively, in week 12.

Incidence of drug-related somnolence by week of treatment



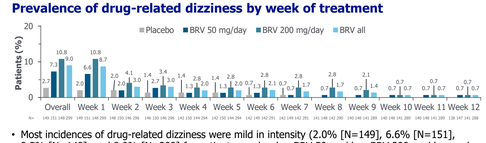
Prevalence of drug-related somnolence by week of treatment



- Most incidences of drug-related somnolence were mild in intensity (6.7% [N=149], 8.6% [N=151], 14.9% [N=148], and 11.7% [N=299] for patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively). No patients reported severe drug-related somnolence.
- For patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively, the mean time from administration to first onset of drug-related somnolence was 17.6, 2.6, 2.0, and 2.2 days (median: 9.0, 1.0, 0.0, and 0.0 days; n=11, 14, 27, 41, respectively).

Incidence of drug-related dizziness by week of treatment

Prevalence of drug-related dizziness by week of treatment



- Most incidences of drug-related dizziness were mild in intensity (2.0% [N=149], 6.6% [N=151], 9.5% [N=148], and 8.0% [N=299] for patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively). No patients reported severe drug-related dizziness.
- For patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively, the mean time from administration to first onset of drug-related dizziness was 2.8, 1.6, 0.3, and 0.9 days (median: 1.5, 0.0, 0.0, and 0.0 days; n=4, 11, 16, 27, respectively).

Drug-related somnolence and dizziness by number of concomitant ASMs

- In patients on BRV the incidence of drug-related somnolence and dizziness was generally similar in patients on 1 and 2 concomitant ASMs.
  - For patients on 1 and 2 concomitant ASMs, respectively, the incidence of drug-related somnolence in all patients on BRV was 13.1% (N=99) and 14.0% (N=200); for patients on placebo the incidence was 1.5% (N=67) and 12.2% (N=82), respectively.
  - For patients on 1 and 2 concomitant ASMs, respectively, the incidence of drug-related dizziness in all patients on BRV was 9.1% (N=99) and 9.0% (N=200); for patients on placebo the incidence was 3.0% (N=67) and 2.4% (N=82), respectively.

Resolved outcomes during the 12-week treatment period

- Most incidences of drug-related somnolence and dizziness were resolved during the 12-week treatment period.
  - For patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively, 8/11 (72.7%), 10/14 (71.4%), 16/27 (59.3%), and 26/41 (63.4%) with drug-related somnolence reported a resolved outcome.
  - For patients on placebo, BRV 50 mg/day, BRV 200 mg/day, and BRV all, respectively, 3/4 (75.0%), 10/11 (90.9%), 15/16 (93.8%), and 25/27 (92.6%) with drug-related dizziness reported a resolved outcome.

Conclusions

- In Asian adults with FOS, the incidence of TEAEs and drug-related TEAEs was highest during the first week of adjunctive BRV treatment and decreased thereafter.
- The majority of reported TEAEs and drug-related TEAEs were mild in intensity; no severe drug-related TEAEs were reported.
- Discontinuations due to TEAEs were numerically lower in patients on adjunctive BRV compared with placebo and generally occurred during the first 5 weeks of treatment.
- The incidence of drug-related somnolence and dizziness was highest during the first week of adjunctive BRV treatment and decreased thereafter. Most occurrences of drug-related somnolence and dizziness were resolved during the 12-week treatment period.
- The prevalence of drug-related somnolence and dizziness decreased over time. The decrease in prevalence is attributed to the majority of patients reporting resolved outcomes.
- In patients on BRV, the incidence of drug-related somnolence and dizziness was generally similar in patients on 1 and 2 concomitant ASMs.
- These tolerability data could help inform patient monitoring and treatment decisions.

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Phone: +1-844-599-CARE (2273)

Email: UCBCares@ucb.com

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