

CLINICAL STUDY REPORT SYNOPSIS: N01395

Name of company: UCB Pharma	Individual study table referring to part of the dossier: Not applicable	<i>(For National Authority Use Only)</i>
Name of finished product: Not applicable	Volume: Not applicable	
Name of active ingredient: Brivaracetam	Page: Not applicable	
Title of study: An open-label, multicenter, single-arm study to evaluate the reduction in nonpsychotic behavioral side effects in subjects with epilepsy switching from levetiracetam to brivaracetam due to nonpsychotic behavioral side effects		
Investigator(s): This was a multicenter study in which 12 Investigators enrolled subjects.		
Study site(s): The study was conducted at 31 sites located in North America and Europe (France, Germany, Italy, Spain, and UK)		
Publication(s) (reference[s]): none		
Study period: 1 year and 4 months		Phase of development: Phase 3b
First subject enrolled: 16 Jul 2012		
Last subject completed: 15 Nov 2013		
<p>Objective(s): The primary objective was to evaluate the reduction of nonpsychotic behavioral side effects in subjects with epilepsy who switched to brivaracetam (BRV) 200mg/day after discontinuing levetiracetam (LEV) 1g/day to 3g/day due to these nonpsychotic behavioral side effects.</p> <p>The secondary objectives were:</p> <ul style="list-style-type: none"> • To evaluate the reduction in intensity of nonpsychotic behavioral side effects in subjects with epilepsy who switched to BRV 200mg/day after discontinuing LEV use due to these nonpsychotic behavioral side effects • To evaluate the efficacy of BRV compared to a retrospective Baseline • To assess the overall safety and tolerability of BRV 200mg/day as adjunctive treatment in adult subjects with epilepsy after they have switched from LEV to BRV treatment <p>The exploratory objectives were:</p> <ul style="list-style-type: none"> • To assess the effects of BRV on subjects' Health-Related Quality of Life (HRQoL) • To obtain a description of subjects' self-reported health status 		

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Methodology: This was an open-label, multicenter, therapeutic study to evaluate the reduction in nonpsychotic behavioral side effects in subjects with epilepsy who switched to BRV 200mg/day after discontinuing LEV use due to these side effects.

The study target population was adult subjects (≥ 16 years of age) with epilepsy currently treated with 2 to 3 antiepileptic drugs (AEDs), including LEV, who had developed nonpsychotic behavioral side effects following the introduction of LEV and who had needed to discontinue LEV due to these side effects. Subjects under 18 years of age could be included only where legally permitted and ethically accepted.

Prior to switching from LEV treatment to BRV, the subject had a Baseline consisting of the documentation and collection of retrospective and prospective safety and efficacy data. For seizure counts, the Baseline was the 4 weeks preceding Visit (V) 2. For nonpsychotic behavioral side effects, the Baseline started with the date of the first LEV dose that was within the approved therapeutic range of 1g/day to 3g/day (maximum of 16 weeks prior to V1) and continued until the end of the study Screening Period (V2).

The maximum duration of the study was up to 19 weeks, with a maximum of 16 weeks of exposure to BRV, which consisted of a maximum 1-week Screening Period and a 12-week Treatment Period. At the end of the Treatment Period, the subject either entered the long-term follow-up (LTFU) study (N01372) or was down-titrated.

Number of subjects (planned and analyzed): Due to the exploratory nature of the study, the sample size was not based on any statistical calculation. To allow for the possibility that some subjects would not qualify for the primary analysis, a total of 32 subjects were to enter the BRV Treatment Period with the expectation that at least 30 subjects would receive at least 1 dose of study drug.

In Oct 2013, the Sponsor evaluated the study in light of the recruitment rate. Given the unanticipated lack of recruitment during the prior 8 weeks, a decision was made to stop recruitment as of 16 Oct 2013.

In total, 32 subjects were screened and 29 (of 30 planned) subjects were enrolled. The stop in recruitment was not due to any safety or compliance concern and the stoppage did not affect the safety of the already enrolled subjects or the scientific quality of the study.

All 29 subjects received at least 1 dose of BRV. The slightly lower sample size was considered as insignificant and was not anticipated to have any effect on the planned analyses, as no statistical hypothesis testing was planned for this study. The ongoing subjects continued in the study as per the current protocol.

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<p>Diagnosis and main criteria for inclusion: This study enrolled male or female subjects (16 years or older) with well-characterized epilepsy according to the 1989 International League Against Epilepsy classification. Subjects must have received LEV at the recommended therapeutic dose (from 1g/day to 3g/day) for up to 16 weeks prior to V1. Following the introduction of LEV, the LEV-treated subject must have had nonpsychotic behavioral side effects due to its introduction and in the opinion of the Investigator, LEV was to be discontinued as a result. Subjects must have been treated with 2 to 3 AEDs, including LEV. Vagal nerve stimulation (VNS) was allowed provided it was implanted for at least 9 months prior to V1 and it would be counted as a concomitant AED. Subjects must have been taking the permitted AEDs (with the exception of LEV) and VNS at a stable and optimal dose from at least 4 weeks before V1 (12 weeks for phenobarbital, phenytoin, and primidone), and the doses were expected to be kept stable during the Screening and Treatment Period.</p> <p>Subjects must not have had seizures that could not have been reliably counted on a regular basis due to their fast and repetitive occurrence (clusters or flurries) and subjects must not have had a history or presence of status epilepticus during the year preceding V1 or during the Screening Period.</p>		
<p>Test product, dose(s) and mode of administration, batch number(s): Brivaracetam was administered orally in a tablet formulation:</p> <ul style="list-style-type: none"> • BRV 10mg tablets (batch number: BX1007336) • BRV 25mg tablets (batch number: BX1007337) 		
<p>Duration of treatment: The maximum duration of the study was up to 19 weeks, with a maximum of 16 weeks of exposure to BRV, which consisted of a maximum 1-week Screening Period and a 12-week Treatment Period. At the end of the Treatment Period, the subject either entered the DTFU study (N01372) or was down-titrated.</p>		
<p>Reference therapy, dose(s) and mode of administration, batch number(s): none.</p>		
<p>Criteria for evaluation:</p> <p>Safety: The primary variable was the percentage of subjects who achieved a clinically meaningful reduction of nonpsychotic behavioral side effects from study entry to the end of the Treatment Period, based on the Investigator's overall assessment.</p> <p>The secondary safety variables included:</p> <ul style="list-style-type: none"> • Shift in the maximum side effect intensity from Baseline to the end of the Treatment Period for side effects primarily associated with discontinuation of LEV, as determined by the 		

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<p>Investigator</p> <ul style="list-style-type: none"> Investigator Global Evaluation of nonpsychotic Behavioral Side Effects (I-GEBSE) Complete abatement of nonpsychotic behavioral side effects at the end of the Treatment Period, based on the Investigator's overall assessment Freedom from nonpsychotic behavioral side effects over the Treatment Period Occurrence of a treatment-emergent adverse event (TEAE) Withdrawal due to an adverse event (AE) Occurrence of a serious adverse event (SAE) <p>The other safety variables included:</p> <ul style="list-style-type: none"> Laboratory tests (blood chemistry, hematology, urinalysis) Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate) Electrocardiogram (ECG) Physical and neurological examination <p>Efficacy:</p> <p>The secondary efficacy variables included:</p> <ul style="list-style-type: none"> Partial-onset seizure (POS) frequency during the Treatment Period for subjects with focal epilepsy Generalized seizure days during the Treatment Period for subjects with idiopathic generalized epilepsy <p>Other efficacy variables included:</p> <ul style="list-style-type: none"> Seizure freedom (all seizure types) during the 12-week Treatment Period Change in Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P) scores from Baseline to the last Treatment Period assessment Patient Global Evaluation Scale (P-GES) at the end of the Treatment Period Investigator Global Evaluation Scale (I-GES) at the end of the Treatment Period 		

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Statistical methods: <p>No statistical hypothesis testing was performed for either the primary or secondary safety variables.</p> <p>To be considered a success for the primary analysis, a subject had to be identified by the Investigator as achieving a clinically meaningful reduction in nonpsychotic behavioral side effects from Baseline to the last assessment during the Treatment Period. The number and percentage of such subjects were summarized for the Full Analysis Set (FAS).</p> <p>A supportive analysis of subjects achieving a clinically meaningful reduction in nonpsychotic behavioral side effects from Baseline to the last assessment during the Treatment Period was conducted for the Per-Protocol Set (PPS). An exploratory analysis that classified discontinuations due to lack of efficacy or AE as treatment failures was conducted.</p>		
Summary and conclusions: <p>Subject disposition: A total of 29 subjects were enrolled instead of 30 subjects as per the protocol; recruitment was stopped 2 months after the 29th subject enrolled. The vast majority of subjects completed the study (26 subjects [89.7%]) and 3 subjects (10.3%) discontinued the study early due to AEs (2 subjects [6.9%]) and lack of efficacy (1 subject [3.4%]).</p>		
Safety results: <p>A summary of the primary safety analysis:</p> <ul style="list-style-type: none"> • A clinically meaningful reduction in the primary nonpsychotic behavioral side effects (nonpsychotic behavioral side effects that led to the discontinuation of LEV) was reported, by the Investigators, for the majority of the subjects who switched from LEV to BRV (27 subjects [93.1%]). • Both the PPS (supportive; 23 of 24 subjects [95.8%]) and FAS (sensitivity; 25 of 29 subjects [86.2%]) analyses support the above result. <p>A summary of the secondary safety analyses also showed positive results in the improvement of nonpsychotic behavioral side effects after subjects switched from LEV to BRV, as described below:</p> <ul style="list-style-type: none"> • At the end of the Treatment Period, the primary nonpsychotic behavioral side effects had been resolved for over half of the subject population (19 subjects [65.5%]) after switching to BRV. In addition, almost all subjects had an improvement in the intensity of their primary nonpsychotic behavioral side effects and no subjects experienced a worsened intensity from 		

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<p>Baseline.</p> <ul style="list-style-type: none"> The majority of subjects had an improvement in their nonpsychotic behavioral side effects in the opinion of the Investigator, with over half of the subject population showing either marked or moderate improvement in the I-GEBSE (20 subjects [69.0%]). One subject (3.4%) had a slight worsening and 1 subject (3.4%) had a marked worsening in the I-GEBSE. At the end of the Treatment Period, the majority of subjects (18 subjects [62.1%]) showed complete abatement of all primary nonpsychotic behavioral side effects (defined as the ending of all nonpsychotic behavioral side effects during the study [ie, the events could be ongoing at the beginning of the treatment period and ended during the treatment period]), of which 3 subjects (10.3%) had freedom from nonpsychotic behavioral side effects (defined as not having any nonpsychotic behavioral side effects at any time throughout the Treatment Period). Complete abatement was reported for over half of the primary nonpsychotic behavioral side effects (33 of 55 [60.0%]). During the Treatment Period, the majority of subjects (22 subjects [75.9%]) recorded a decrease in the total number of nonpsychotic behavioral side effects with 16 subjects with POS (of the 22 recorded at Baseline) and 8 subjects with generalized seizures (of the 9 recorded at Baseline). There were no notable differences observed based on Baseline seizure type. Both the number of subjects who had primary nonpsychotic behavioral side effects and the number of events decreased as the study progressed. Following the initiation of BRV, 27 of the 55 primary nonpsychotic behavioral side effects were resolved following the administration of BRV (note: resolution is defined as [date of last reported occurrence – date of first dose of BRV]+1). The median time to the resolution of the primary nonpsychotic behavioral side effects was 15 days (mean [standard deviation; SD]: 22.9 days [\pm20.5]). A total of 23 subjects experienced at least 1 TEAE (79.3%; 67 events) and the commonly reported TEAEs included headache, fatigue, and back pain. All but 1 TEAE was reported during the Treatment Period; 1 event of complex partial seizure was reported during the Down-Titration Period. The majority of TEAEs experienced were of moderate intensity (12 subjects [41.4%]) and the TEAEs that were of severe intensity (3 subjects [10.3%]) were back pain, bacterial test, crystal urine present, fatigue, headache, lymphocyte count decreased, neutrophil count 		

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increased, tooth abscess, and white blood cell count increased. A small proportion of events reported were drug-related TEAEs (13 of the 67 events), in the opinion of the Investigator, which included dizziness, headache, myoclonic epilepsy, and tremor.

- No deaths were reported during the study.
- One subject experienced 2 SAEs of suicidal ideation and suicide attempt (Subject ████████); both events were considered to be not related to the study drug by the Investigator. These events were reported with positive C-SSRS findings.
- A total of 2 subjects experienced TEAEs that led to the discontinuation of the study drug (Subject ████████ and Subject ████████); the events were myoclonic epilepsy, suicidal ideation, and suicide attempt. A total of 16 subjects (55.2%) experienced at least 1 event of TEAE of interest, which included fatigue, depression, dizziness, insomnia, and tremor.

A summary of the other safety variables analyzed:

- During the study, no clinically meaningful findings were reported for hematology, blood chemistry, urinalysis, and physical examination.

Efficacy results:

In summary, administration of BRV reduced seizure frequencies from Baseline (consisting of the documentation and collection of retrospective efficacy data) and resulted in the improvement in the quality of life as described below:

- Control of seizures with BRV was maintained with a numerical reduction in seizure frequency of 3.5 seizures in 28 days.
- The mean increase in the QOLIE-31-P total and subscale scores and the health status score from Baseline to V6 and to the last value indicated that the switch from LEV to BRV for this subject population was associated with an improvement in quality of life; this was found consistently across all scores. All but 2 (Seizure Worry and Social Functioning) of the individual QOLIE-31-P total and subscale scores showed a mean increase of ≥ 10 points on a 100-point scale, with the largest mean (SD) increase observed for Medication Effects to V6 (27.6 [± 25.5]) and to the last value recorded (24.6 [± 27.1]). This change may be related to the relief in the nonpsychotic behavioral side effects experienced by subjects after switching from LEV to BRV. The trend of improvement for both QOLIE-31-P distress and prioritization items was consistent with that of the total and subscale mean scores.
- The majority of subjects experienced an improvement in their epilepsy severity, as

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<p>demonstrated by P-GES and I-GES with a similar level of improvement on both scales. The only slight difference was that more subjects reported no change for P-GES compared to I-GES at both V6 and at the last value recorded.</p>		
<p>Conclusions:</p> <p>In this open-label study with a small subject population (N=29), BRV has demonstrated a positive impact in reducing the nonpsychotic behavioral side effects in subjects with epilepsy who discontinued LEV prior to receiving BRV. This was demonstrated by the clinically meaningful reduction in the nonpsychotic behavioral side effects experienced by the majority of subjects. In addition, based on a retrospective Baseline, the seizure frequency was maintained and BRV appeared to be [REDACTED] and well tolerated. Thus, BRV could be an important treatment option for a physician to consider for this subpopulation of patients with epilepsy, who discontinued LEV treatment due to nonpsychotic behavioral side effects, based on the results observed in this study.</p> <p>In conclusion, the results from this study suggest that patients who experience nonpsychotic behavioral side effects leading to the discontinuation of LEV treatment may benefit from an immediate switch to BRV. However, these results should be interpreted with caution owing to the small sample size, the lack of historic seizure data, and the open-label nature of the study. Further randomized, blinded studies exploring this finding would be of interest.</p> <p>Report date: 05 Aug 2014</p>		