

CLINICAL STUDY REPORT SYNOPSIS: N01253

Name of company: UCB Inc.	Individual study table referring to part of the dossier: Not applicable	<i>(For National Authority Use Only)</i>
Name of finished product:	Volume: Not applicable	
Name of active ingredient: Brivaracetam	Page: Not applicable	
Title of study: An international, double-blind, parallel-group, placebo-controlled, randomized study: evaluation of the efficacy and safety of brivaracetam in subjects (≥ 16 to 70 years old) with partial onset seizures		
Investigator(s): 85 investigators screened subjects for this study		
Study site(s): Multicenter study in North America, South America, and Australia; 85 sites screened at least 1 subject and 72 sites randomized at least 1 subject		
Publication(s) (reference[s]): None at the time of this report.		
Studied period: 23 weeks First subject enrolled: 07 Sep 2007 Last subject completed: 02 Jan 2009	Phase of development: Phase 3, therapeutic confirmatory	
Objective(s): <p>The primary objective of the study was to evaluate the efficacy of brivaracetam (BRV) at doses of 5, 20, and 50mg/day in reducing seizure frequency in subjects with partial onset seizures (POS) not fully controlled despite optimal treatment with 1 to 2 concomitant antiepileptic drug(s) (AED[s]), compared with placebo (PBO).</p> <p>Secondary objectives of the study were:</p> <ul style="list-style-type: none"> • To confirm the dose/clinical response relationship • To assess the effects of BRV on Type IC seizures • To assess the safety and tolerability of BRV • To assess the effects of BRV on different dimensions of patients' functioning and Health-Related Quality of Life (HRQoL) <p>Exploratory objectives of the study were:</p> <ul style="list-style-type: none"> • To obtain a description of the subjects' self-reported health status • To explore direct medical resource use and indirect cost parameters • To explore the population pharmacokinetics of BRV and identify relevant covariates and to assess the impact of BRV on concomitant AED plasma levels 		

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<ul style="list-style-type: none"> To collect blood samples for genotyping of SV2- and epilepsy-related genes (for a pooled analysis at the program level) 		
<p>Methodology: This was a 23-week, Phase 3, double-blind, parallel-group, placebo-controlled, randomized study conducted in 400 randomized subjects to determine efficacy and safety of BRV in subjects (≥ 16 to 70 years old) with POS. Subjects were enrolled and entered an 8-week Baseline Period. At the end of the Baseline Period, subjects were randomized in a 1:1:1:1 fashion to 1 of 4 treatment arms (BRV 5mg/day, 20mg/day, 50mg/day, or PBO). Oral tablets of BRV (2.5mg/day, 10mg/day, and 25mg/day) and matching PBO were used in the study. Subjects were randomized to the full-dose, without any Titration Phase. The Treatment Period lasted 12 weeks. The daily dose was administered in 2 equal intakes, morning and evening. One fallback option was offered. At the end of the Treatment Period, the subject either entered a long-term follow-up (LTFU) study at a recommended starting dose of 50mg/day, or entered a Down-Titration Period of 1 week followed by a 2-week Study Drug-free Period.</p>		
<p>Number of subjects (planned and analyzed): 400 subjects (100 subjects per arm) were planned; a total of 509 subjects were screened and 400 subjects were randomized</p>		
<p>Diagnosis and main criteria for inclusion:</p> <ol style="list-style-type: none"> Subjects were 16 to 70 years, both inclusive. Subjects under 18 years of age were only included where legally permitted and ethically accepted. Subjects had well-characterized focal epilepsy or epileptic syndrome according to the International League Against Epilepsy (ILAE) classification (Commission on Classification and Terminology of the ILAE, 1989). Subjects had a history of POS whether or not secondarily generalized (Type I seizures according to the ILAE classification). Subjects who had at least 2 POS whether or not secondarily generalized per month during the 3 months preceding Visit 1 (V1). Subjects who had at least 8 POS whether or not secondarily generalized during the 8-Week Baseline Period. Subjects were uncontrolled while treated by 1 to 2 permitted concomitant AED(s). Vagal nerve stimulation (VNS) was allowed and was not counted as a concomitant AED. 		

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Main criteria for exclusion: <ol style="list-style-type: none"> History or presence of seizures occurring only in clusters (too frequently or indistinctly separated to be reliably counted) before Visit 3. History or presence of status epilepticus during the year preceding Visit 1 or during Baseline. 		
Test product, dose(s) and mode of administration, batch number(s): Brivaracetam was supplied as white, [REDACTED] tablets 2.5mg, 10mg, and 25mg. Batch numbers: BRV 2.5mg (15343, 15524), BRV 10mg (15527, 15528, 15801), and BRV 25mg (15216, 15451)		
Duration of treatment: The total duration of the study was up to 23 weeks by subject with a maximum 13-week exposure to BRV: Baseline Period (8 weeks), Treatment Period (12 weeks), Down-titration Period (1 week), Study Drug-Free Period (2 weeks)		
Reference therapy, dose(s) and mode of administration, batch number(s): Matching PBO was supplied as white, [REDACTED] tablets 2.5mg, 10mg, and 25mg. Batch numbers: PBO 2.5mg (15127, 15345, 16015), PBO 10mg (15802, 15944, 16089), and PBO 25mg (15069, 15943)		
Criteria for evaluation: Efficacy: The primary efficacy variable was the POS (Type I) frequency per week over the Treatment Period. The secondary efficacy variables included: <ul style="list-style-type: none"> • Responder rate (the proportion of subjects who had a $\geq 50\%$ reduction in seizure frequency per week from Baseline) for POS (Type I) over the Treatment Period • All seizure frequency (Type I + II + III) per week over the Treatment Period • Percent reduction for POS (Type I) frequency per week from Baseline to the Treatment Period • Categorized percentage reduction from Baseline in seizure frequency for POS (Type I) over the Treatment Period - The categories include: $< -25\%$, -25% to $< 25\%$, 25% to $< 50\%$, 50% to $< 75\%$, 75% to $< 100\%$, and 100% • Seizure freedom rate (all seizure types) over the Treatment Period 		

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<ul style="list-style-type: none"> • Time to nth (n=1, 5, 10) Type I seizure during the Treatment Period • Reduction of seizure frequency ratio (Type IC/Type I) from Baseline to the Treatment Period • Total Patient Weighted Quality of Life Inventory in Epilepsy-Form 31 (QOLIE-31-P) score • Seizure Worry QOLIE-31-P score • Daily Activities/Social Functioning QOLIE-31-P score • Remaining QOLIE-31-P domain scores (Energy/Fatigue, Emotional Well-being, Cognitive Functioning, Overall Quality of Life, and Medication effects) • Hospital Anxiety and Depression Scale (HADS) scores (Anxiety, Depression) • Patient's Global Evaluation Scale (P-GES) • Investigator's Global Evaluation Scale (I-GES) <p>Exploratory efficacy variables included:</p> <ul style="list-style-type: none"> • EuroQoL-5 dimensions (EQ-5D) items • Direct cost parameters: concomitant medications, medical procedures, healthcare provider consultations not foreseen by the protocol, hospitalizations • Indirect cost parameters: number of working or school days lost by the subject and/or caregiver • Socioprofessional data (driver's license, employment status) 		
Pharmacokinetics/pharmacodynamics: The pharmacokinetic variables included: <ul style="list-style-type: none"> • BRV (parent compound only) plasma levels • Concomitant AED (and/or relevant metabolites) plasma levels 		

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Safety: The safety variables included: <ul style="list-style-type: none"> • Adverse event (AE) reporting • Clinical laboratory evaluations (including blood and urine) • Vital signs (including orthostatic measurements) and physical examination findings • Electrocardiogram (ECG) • Body weight 		
Statistical methods: The primary efficacy variable was the POS (Type I) frequency per week over the Treatment Period. It was calculated for each subject in the Modified Intent-to-Treat (mITT) Population as: $\frac{\text{Total number of Type I seizures over the Treatment Period}}{\text{Total number of days with no missing seizure count in the Treatment Period}} \times 7$ <p>This variable was transformed prior to being analyzed using the logarithmic transformation $\log_e [x+1]$ (where x is the seizure frequency per week). The log-transformed POS frequency per week over the Treatment Period was analyzed applying an analysis of covariance (ANCOVA) model, including treatment and a stratification effect combining study region and concomitant levetiracetam (LEV) use (as described below, based on data as recorded in the case report form as factors and the log-transformed Baseline seizure frequency per week as covariate).</p> <p>It was planned that the 3 doses of BRV would be tested at the 5% significance level against PBO, according to a predefined hierarchical sequential rejective testing procedure. For Step 1, the hierarchical testing procedure began with the BRV 50mg/day dose versus PBO. If the comparison was not statistically significant, the procedure stopped and no groups were declared different from PBO. If the comparison was statistically significant, the BRV 50mg/day group was considered different from PBO and the procedure continued with the second step. Step 2 tested the BRV 20mg/day dose against PBO in a similar manner to Step 1, and if the comparison was statistically significant, Step 3 tested BRV 5mg/day against PBO. This procedure strongly controlled the overall Type I error rate to 0.05.</p>		

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Summary and conclusions:

Subject disposition: A total of 509 subjects were screened and 109 of these subjects were screen failures. The most common reasons for screen failure were ineligibility (83 of 109 subjects) and withdrawal of consent for personal reasons (12 of 109 subjects). The remaining 400 subjects were randomized to receive PBO or BRV (5mg/day, 20mg/day, or 50mg/day). Four subjects were excluded from the Intent-to-Treat (ITT) Population due to failure to take study medication and randomization errors. Thus, 396 subjects were included in the ITT Population. The Safety Population was comprised of the same set of subjects as the ITT Population. The (mITT) Population was defined as all subjects in the ITT Population with the exception of 3 subjects excluded due to serious, persistent compliance issues involving 1 study site and 1 subject excluded due to an extremely high seizure frequency (>100/day) prior to and during the study. Thus, a total of 392 subjects were included in the mITT Population. Overall, 91.2% of subjects completed the study and 87.6% of these entered the LTFU; 8.8% of subjects discontinued the study. The rate of study completion and discontinuation was similar across most treatment groups (5.1% in the PBO group, 7.0% in the BRV 20mg/day group, and 7.9% in the BRV 50mg/day group), but slightly higher in the BRV 5mg/day group (15.5%). The most common reason for discontinuation was AE (5.3%).

Efficacy results: For the primary efficacy variable, the BRV 50mg/day group showed a reduction in log-transformed POS frequency per week of 12.8% over PBO (p=0.025); thus, this study achieved its primary endpoint. Statistical significance was not observed for the BRV 20mg/day or BRV 5mg/day groups for the primary efficacy variable.

Similar positive findings were seen in the responder analysis (50% reduction in weekly POS frequency from Baseline to the Treatment Period) and in the median percent reduction from Baseline in POS frequency per week. A statistically greater proportion of subjects in the BRV 50mg/day group (32.7%) were 50% responders compared with the PBO group (16.7%; p=0.008). The median percent reduction from Baseline was 30.47% with BRV 50mg/day and 17.75% with PBO (p=0.003). Additionally, 4 subjects receiving BRV 50mg/day were seizure free for the entire Treatment Period compared with 0 subjects receiving PBO.

The results of all other secondary efficacy analyses were consistent with the primary analysis.

Primary ANCOVA analysis of the log-transformed POS frequency per week over the Treatment Period, including a treatment by-concomitant LEV use interaction term, showed that the treatment-by-concomitant LEV use interaction was not significant at the 0.10 level,

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as specified in the SAP (p=0.549). Despite this nonsignificant interaction, results of the primary analysis showed that subjects in the BRV 50mg/day group without concomitant LEV use showed a 16.0% reduction over PBO; no treatment effect was observed in subjects in the BRV 50mg/day group with concomitant LEV use (-0.9%).

Primary ANCOVA analysis of the log-transformed POS frequency per week over the Treatment Period, including a treatment-by-region interaction term, showed that the treatment-by-region interaction was not significant at the 0.10 level, as specified in the SAP (p=0.310). The treatment effect (percent reduction over PBO) with BRV for the primary efficacy analysis of POS frequency per week was highest in both regions (North America/Australia [NAA]=8.9%; Latin America [LA]=18.1%) in subjects receiving BRV 50mg/day. Results of the secondary endpoints for 50% responders and median percent reduction from Baseline were generally consistent with the primary efficacy analysis.

There were no meaningful differences in HRQoL or indirect or direct cost parameters between any BRV dose group and PBO.

Pharmacokinetics/pharmacodynamics results: These results are presented in a separate report.

Safety results: Overall, 75.8% of subjects receiving BRV experienced at least 1 treatment-emergent adverse event (TEAE) during the Treatment Period compared with 70.4% receiving PBO. The most common AEs with BRV compared with PBO were somnolence (15.1% vs 7.1%), dizziness (14.1% vs 9.2%), headache (10.1% vs 14.3%), influenza (6.4% vs 1.0%), nausea (5.7% vs 3.1%), and fatigue (8.7% vs 2.0%). No clear dose-response was observed in incidence of TEAEs across BRV dose groups.

The majority of TEAEs reported during this study were mild or moderate in intensity. Drug-related TEAEs per the Investigator were reported in 48.7% of subjects receiving BRV and 35.7% receiving PBO; a possible dose-related increase of drug-related TEAE incidence was observed in the BRV groups. The incidence of TEAEs that led to permanent study drug discontinuation was higher in BRV groups compared with the PBO group (2.0%, 8.2%, 5.0%, and 5.9% in the PBO, BRV 5mg/day, BRV 20mg/day, and BRV 50mg/day groups, respectively). Treatment-emergent AEs that led to permanent study drug discontinuation during the Overall Period were most frequently reported in the psychiatric disorders System Organ Class (SOC). Six subjects receiving BRV experienced a nonfatal SAE during the Treatment Period while no SAEs were reported in subjects receiving PBO. Two deaths occurred, one in a subject receiving BRV 20mg/day and one in a subject receiving BRV 50mg/day. The Investigator reported respiratory failure and

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aspiration bronchial as the cause of death for the subject receiving BRV 20mg/day and autopsy revealed general brain hypoxia for the subject receiving BRV 50mg/day.

The incidence of TEAEs during the Treatment Period was similar in the subjects with concomitant LEV use (73.7% of PBO subjects and 73.7% of BRV subjects) and in the subjects without concomitant LEV use (69.6% of PBO subjects and 75.5% of BRV subjects).

Several UCB SOC's and UCB grouping terms of special interest were evaluated during this study. There were no clinically meaningful differences in the TEAEs of special interest in these UCB SOC's (blood and lymphatic disorders, nervous system disorders, psychiatric disorders, and hepatobiliary disorders) or UCB grouping terms (cardiac arrhythmias, vision disorders, skin reactions, vascular haemorrhagic disorders, and chemical injury, overdose, poisoning).

There were no clinically meaningful changes from Baseline to the last value in the Treatment Period for hematology, blood chemistry, or urinalysis parameters. There were no meaningful trends in the number of subjects who shifted from normal at Baseline to abnormal during the study for any laboratory parameters. Overall, the percentage of subjects with possibly clinically significant (PCS) laboratory values was low and similar among treatment groups. There were no clinically relevant changes in vital signs or ECG abnormalities. There were no clinically meaningful differences in physical or neurological exam findings, in psychiatric or mental status, or in the number of concurrent medical procedures during this study across treatment groups.

This document cannot be used to support any marketing authorization application and any extensions or variations thereof.

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Conclusions: <ul style="list-style-type: none"> For the primary efficacy variable, the BRV 50mg/day group showed a statistically significant reduction in POS frequency per week of 12.8% over PBO (p=0.025); thus, this study achieved its primary endpoint. Statistical significance was not observed for the BRV 20mg/day or BRV 5mg/day groups for the primary efficacy variable. Secondary efficacy analyses for 50% responder rate, median percent reduction from Baseline, and categories of response rates were consistent with the primary analyses. A statistically greater proportion of subjects in the BRV 50mg/day group (32.7%) were 50% responders compared with the PBO group (16.7%; p=0.008). The median percent reduction from Baseline was 30.47% with BRV 50mg/day and 17.75% with PBO (p=0.003). Brivaracetam at doses of 5mg/day, 20mg/day, and 50mg/day was generally well tolerated compared with PBO in this controlled study of subjects aged 16 to 70 years old with POS. Report date: 03 Jun 2011		