CLINICAL STUDY REPORT SYNOPSIS: N01252

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:**	*(For National Authority Use Only)*
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Title of study: A multi-center, 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): 76 Investigators screened subjects for this study

Study site(s): Multicenter study in Europe and India; 76 sites screened at least 1 subject and 71 sites randomized at least 1 subject

Publication(s) (reference[s]): None at the time of this report.

Studied period: 24 weeks **First subject enrolled:** 10 Sep 2007 **Last subject completed:** 09 Feb 2009	**Phase of development:** Phase 3, therapeutic confirmatory

Objective(s):

The primary objective of the study was to evaluate the efficacy of brivaracetam (BRV) at doses of 20, 50, and 100mg/day in reducing seizure frequency in subjects with partial-onset seizures (POS) not fully controlled despite optimal treatment with 1 to 2 concomitant anti-epileptic drugs (AEDs), compared with placebo (PBO).

Secondary objectives of the study were:

- 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

Exploratory objectives of the study were:

- To obtain a description of the subjects' self-reported health status
- To explore direct medical resources 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
- To collect blood samples for genotyping of SV2-and epilepsy-related genes (for a pooled analysis at the program level)

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Methodology: This was a 24-week, Phase 3, therapeutic confirmatory, double-blind, parallel-group, PBO-controlled, randomized study conducted in 399 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 20mg/day, 50mg/day, 100mg/day, or PBO). A 1:1:1:1 central randomization (random permuted blocks) stratified per geographical region (Eastern Europe, Western Europe, India) and for the use of levetiracetam (LEV; with or without concomitant LEV use at study entry) was used in the study to ensure overall balance across the different treatment groups. Oral tablets of BRV (10mg and 25mg) 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 BRV 50mg/day, or entered a Down-Titration Period of 2 weeks followed by a 2-week Study Drug-Free Period.

Number of subjects (planned and analyzed): 400 subjects (100 subjects per arm) were planned; a total of 486 subjects were screened and 399 subjects were randomized

Diagnosis and main criteria for inclusion:

1. Subjects were from 16 to 70 years, both inclusive. Subjects under 18 years of age were only included where legally permitted and ethically accepted.
2. Subjects with well-characterized focal epilepsy or epileptic syndrome according to the International League Against Epilepsy (ILAE) classification
3. Subjects had a history of POS whether or not secondarily generalized (Type I seizures according to the ILAE classification).
4. Subjects had at least 2 POS whether or not secondarily generalized per month during the 3 months preceding Visit 1.
5. Subjects had at least 8 POS whether or not secondarily generalized during the 8-Week Baseline Period.
6. Subjects were uncontrolled while treated by 1 to 2 permitted concomitant AED(s). Vagal nerve stimulation was allowed and was not counted as a concomitant AED.

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Main criteria for exclusion:

1. History or presence of seizures occurring only in clusters (too frequently or indistinctly separated to be reliably counted) before Visit 3.
2. 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 10mg and 25mg. Batch numbers: BRV 10mg (15527, 15801, 15938), BRV 25mg (14916, 15451)

Duration of treatment: The total duration of the study was up to 24 weeks by subject with a maximum 14-week exposure to BRV: Baseline Period (8 weeks), Treatment Period (12 weeks), Down-Titration Period (2 weeks), 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 10mg and 25mg. Batch numbers: PBO 10mg (15529, 15944, 15945), 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:

- Responder rate (the proportion of subjects who had a ≥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
- Time to n^{th} (n=1, 5, 10) Type I seizure during the Treatment Period

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- Reduction of seizure frequency ratio (Type IC/Type I) from Baseline to the Treatment Period
- Total Patient Weighted Quality of Life in Epilepsy Inventory-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)

Exploratory efficacy variables included:

- 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, etc)

Pharmacokinetics/pharmacodynamics:

The pharmacokinetic variables included:

- BRV (parent compound only) plasma levels
- Concomitant AED (and/or relevant metabolites) plasma levels

Safety:

The safety variables included:

- Adverse event (AE) reporting
- Clinical laboratory evaluations (including blood and urine)

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- 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 intent-to-treat (ITT) Population as:

$$\frac{Total\ number\ of\ Type\ I\ seizures\ over\ the\ Treatment\ Period}{Total\ number\ of\ days\ with\ no\ missing\ seizure\ count\ in\ the\ Treatment\ Period} \times 7$$

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 LEV use (as recorded in the case report form) as factors and the log-transformed Baseline seizure frequency per week as covariate.

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 PBO against BRV 100mg/day dose in a similar manner to Step 1, and if the comparison was statistically significant, Step 3 tested PBO against BRV 20mg/day. This procedure strongly controlled the overall Type I error rate to 0.05.

Summary and conclusions:

Subject disposition: A total of 486 subjects were screened and 87 of these subjects were screen failures. The most common reasons for screen failure were ineligibility (62 of 87 subjects) and withdrawal of consent for personal reasons (not related to AEs) (15 of 87 subjects). The remaining 399 subjects were randomized to receive PBO or BRV (20mg/day, 50mg/day, or 100mg/day). One subject randomized to the BRV 50mg/day group died before consuming any study drug; this subject was excluded from the ITT Population. Thus, 398 subjects were included in the ITT Population. The Safety Population was comprised of the same set of subjects as the ITT Population.

Overall, 92% of subjects completed the study, and 87% of these continued in the

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LTFU study; 7.8% of subjects discontinued the study and the most common reason for discontinuation was AE (4.8%). The rate of study completion and discontinuation was similar across treatment groups.

Efficacy results:

The primary outcome for study N01252 did not achieve statistical significance based on the sequential testing procedure, which required statistical significance at the 0.050 level for BRV 50mg/day versus PBO prior to the testing of BRV 100mg/day and BRV 20mg/day in sequence. For the primary efficacy variable, the BRV 50mg/day group showed a reduction in log-transformed POS frequency per week of 6.5% over PBO; however, this reduction was not statistically significant (p=0.261), therefore this study did not achieve its primary endpoint. Further sensitivity analyses (Linear Effects Mixed Model, rank-ANCOVA, and primary ANCOVA analysis on Per-Protocol Population) were consistent with the primary analysis. For BRV 50mg/day, 27.3% of subjects achieved a 50% response rate compared with 20.0% for PBO, while the median percent reduction from Baseline was 26.83% compared with 17.03% for PBO.

Although the primary outcome for N01252 did not achieve statistical significance based on the sequential testing procedure to control for multiplicity, the comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome (p=0.037). The secondary endpoints were consistent with the primary endpoint, with statistical significance achieved with BRV 100mg/day versus PBO for the 50% responder rate (36.0% vs 20.0%, p=0.023) and median percent reduction from Baseline (32.45% vs 17.03%, p=0.004), respectively. Additionally, 4 subjects receiving BRV 100mg/day were seizure free for the entire Treatment Period compared to 0 subjects receiving PBO.

There were no meaningful differences in health-related quality of life or indirect or direct cost parameters between any BRV dose group and PBO. With respect to other exploratory variables, no meaningful trends were noted.

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

Safety results:

The incidence of treatment-emergent AEs (TEAEs) in the Treatment Period was slightly higher in the BRV overall group (60.7%) compared with the PBO group (53.0%); the incidence of TEAEs was similar between BRV dose groups. Treatment-emergent AEs were most frequently reported in the nervous system disorders system organ class (SOC) for all

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treatment groups. The most common TEAEs (ie, those occurring in ≥5% of subjects in the BRV overall group or the PBO group) during the Treatment Period were: headache (13.8% vs 9.0%), somnolence (7.4% vs 6.0%), dizziness (5.7% vs 5.0%), and fatigue (5.0% vs 2.0%), respectively. Of these, the only TEAEs that occurred at a ≥3% higher incidence in the BRV overall group compared with the PBO group were headache and fatigue. The majority of TEAEs reported during the Treatment Period were mild or moderate in intensity; a similar incidence of severe TEAEs was observed across treatment groups (~4% of subjects). The most frequently reported TEAEs occurring within 7 days of initiation of study drug in the BRV overall group were somnolence (3.7%), headache (3.0%), dizziness (2.3%), and fatigue (2.3%); the incidences of these TEAEs were low and similar between treatment groups.

The incidence of drug-related TEAEs during the Treatment Period was similar between the PBO (31.0%) and BRV overall group (34.2%); a possible dose-related trend was observed in the BRV groups. The most frequently reported drug-related TEAEs in the BRV overall group compared with the PBO group were as follows: headache (6.4% vs 3.0%), somnolence (6.4% vs 6.0%), and fatigue (4.7% vs 2.0%).

The incidence of TEAEs during the Treatment Period was higher in the subjects with concomitant LEV use for both the PBO and BRV overall treatment groups (66.7% and 72.4%, respectively) compared with subjects without concomitant LEV use (50.0% and 57.9%, respectively).

The incidence of TEAEs in the Overall Period that led to permanent study drug discontinuation was similar in the BRV overall group (4.7%) compared with PBO (4.0%). Treatment-emergent AEs that led to permanent study drug discontinuation were most frequently reported in the UCB SOC of psychiatric disorders; the most frequently reported preferred term was aggression (reported in 3 subjects).

The incidence of serious AEs (SAEs) in the Overall Period was higher in the PBO group (6.0%) than in the BRV overall group (2.3%). One subject in the PBO group died during this study and 1 subject died prior to consuming study drug.

Several UCB SOCs 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 SOCs (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).

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There were no clinically meaningful changes from Baseline to the last value in the Treatment Period for hematology, blood chemistry, or urinalysis parameters. Small decreases in mean white blood cell count and neutrophil count were observed in the BRV dose groups compared with the PBO group. 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.

The incidence of potentially clinically significant (PCS) hematology, blood chemistry, and urinalysis values was generally similar across treatment groups during the Treatment Period with a few exceptions. More subjects in the BRV overall group experienced PCS values of low hematocrit (5.7%) compared with PBO (3.0%). A higher incidence of PCS high gamma-glutamyl transferase values was observed for the BRV overall group (2.3%) compared with PBO (0%). Slightly higher incidences of PCS urine parameters were observed in the BRV overall group compared with the PBO group for: blood urine (14.2% vs 9.1%, respectively), white blood cell urine (13.3% vs 9.4%, respectively), and bacteria urine (22.2% vs 15.6%, respectively).

There were no clinically meaningful changes from Baseline to the last value in the Treatment Period for vital sign parameters. The incidence of PCS vital sign values was generally similar across the treatment groups. There were no TEAEs associated with PCS vital sign values with the exception of TEAEs of weight increased and weight decreased, all of which were mild or moderate in intensity and did not result in a change in study drug dose.

There were no clinically meaningful differences in ECG status from Baseline to the last visit on treatment across treatment groups. One subject in the BRV 50mg/day group had a treatment-emergent clinically significant ECG abnormality of significant Q-wave and ST segment elevation. No TEAEs were associated with any 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.

Conclusions:

- The primary efficacy outcome did not achieve statistical significance. The BRV 50mg/day group showed a reduction in log-transformed POS frequency per week of 6.5% over PBO (p=0.261). For BRV 50mg/day, 27.3% of subjects achieved a 50% response compared to 20.0% for PBO, while the median percent reduction from Baseline was 26.83% compared to 17.03% for PBO.

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- The comparison of BRV 100mg/day versus PBO was nominally statistically significant with an 11.7% reduction over PBO for the primary outcome (p=0.037). The secondary endpoints were consistent with the primary endpoint, with statistical significance achieved with BRV 100mg/day versus PBO for the 50% responder rate (36.0% vs 20.0%, p=0.023) and median percent reduction from Baseline (32.45% vs 17.03%, p=0.004) respectively. Additionally, 4 subjects receiving BRV 100mg/day were seizure free for the entire Treatment Period compared to 0 subjects receiving PBO.
- Brivaracetam at doses of 20mg/day, 50mg/day, and 100mg/day was generally well tolerated.

Report date: 26 Jul 2010