CLINICAL STUDY REPORT SYNOPSIS: N01276

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
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Title of study: An international, double-blind, randomized, multi-center, parallel group, historical-control conversion to monotherapy study to evaluate the efficacy and safety of brivaracetam in subjects (≥16 to 75 years old) with partial onset seizures with or without secondary generalization.

Investigator(s): Fifty-six Investigators enrolled subjects in this study.

Study site(s): Multicenter study in Australia, Europe, and North America: 56 sites screened at least 1 subject and 41 sites randomized at least 1 subject.

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

Studied period: 31 weeks **First subject enrolled:** 25 Aug 2008 **Last subject completed:** 15 Feb 2010	**Phase of development:** Phase 3, therapeutic confirmatory

Objective(s): The primary objective was to evaluate the efficacy of brivaracetam (BRV) in the conversion to monotherapy at the dose of 50 and 100mg/day (administered in 2 equal doses per day) in subjects with partial onset seizures (POS) when compared to a historical pseudo-placebo control group. This objective was based on the White Paper on Alternative Monotherapy Design in the Treatment of Epilepsy (French et al, 2005).

[Although the primary objective stated in the protocol included BRV 100mg/day, N01276 was designed to evaluate only BRV 50mg/day in comparison to historical control. Brivaracetam 100mg/day was included for the purpose of blinding and consistency with the historical-control study design, which included 2 treatment arms.]

The secondary objective was to assess the safety and tolerability of BRV in subjects undergoing conversion to monotherapy for POS.

The exploratory objectives were:

- To explore direct medical resource use and indirect cost parameters
- To explore the impact of BRV on different patient reported outcomes (PRO): the Quality of Life Inventory in Epilepsy (QOLIE-31-P), the Hospital Anxiety and Depression Scale (HADS), the EuroQoL-5 Dimensions (EQ-5D), and a Patient Global Evaluation Scale (P-GES)
- To explore the impact of BRV on the Investigator Global Evaluation Scale (I-GES)

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- To obtain a description of the subject's self-reported health status
- To explore the population pharmacokinetics of BRV in monotherapy
- To collect blood samples for genotyping of SV2- and epilepsy-related genes (for a pooled analysis at the program level)

Methodology: This was a 31-week, Phase 3, therapeutic confirmatory, international, multicenter, double-blind, randomized, parallel-group, historical-control study designed for subjects (≥16 to 75 years old) with a history of inadequately controlled POS classified as simple or complex, whether or not secondarily generalized.

Subjects were screened and then entered an 8-week Baseline Period during which they were to maintain a stable dose of their current antiepileptic drugs (AED[s]) and keep diaries of their seizure activity. At the end of the Baseline Period, those subjects who met all inclusion/exclusion criteria were randomized to treatment with BRV and entered a 7-day BRV Add-On Period. A 3:1 (BRV 50mg/day:BRV 100mg/day) central randomization (random permuted blocks) was used and stratified as follows: use of levetiracetam (LEV), use of carbamazepine (CBZ) or oxcarbazepine (OXC), and region. At the end of the 7-day BRV-Add-On Period, subjects were to begin tapering Baseline AED(s) to complete withdrawal over an 8-week Period (Baseline AED Tapering Phase). At the end of the Baseline AED Tapering Phase, subjects entered an 8-week Monotherapy Phase. If subjects met predefined exit criteria consistent with those used in historical-control studies, they were permitted to enter a long-term follow-up (LTFU) study, N01315, or were to enter a Reconversion Period (3 to 4 weeks) in which they were converted from BRV to other AEDs followed by a 2-week study drug free Follow-Up Period. Subjects who completed the Monotherapy Phase were also eligible to participate in N01315 (LTFU) or were to enter the Reconversion and Follow-Up Period.

The 4 protocol-defined exit criteria were as follows:

1. At least a doubling in the partial seizure (motor and nonmotor) frequency over a 28 day period as compared to the Baseline Period 28 day partial seizure frequency.
2. At least a doubling in the highest consecutive 2-day partial seizure (motor and nonmotor) frequency that had occurred during the Baseline Period. The following exceptions were applied: if the highest consecutive 2-day seizure frequency during the Baseline Period was 1, reaching Exit Criterion 2 required a tripling of the Baseline Period value, ie, a consecutive 2-day seizure frequency of 3 was required.
3. Occurrence of a generalized tonic-clonic seizure, if none had occurred in the 6 months before randomization.

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4. An episode of status epilepticus, a prolongation of seizure duration, a worsening of seizure frequency, or emergence of a new seizure type considered by the Investigator to require intervention. If a subject required the use of benzodiazepines, specifically due to seizure worsening, the subject met this criterion.

Number of subjects (planned and analyzed): A total of 178 subjects (134 in the BRV 50mg/day group and 44 in the BRV 100mg/day group) were planned for randomization. A total of 164 subjects were screened and 88 subjects (68 in the BRV 50mg/day group and 20 in the BRV 100mg/day group) were randomized. Less than the planned number subjects were enrolled due to premature study termination.

Diagnosis and main criteria for inclusion:

- Subjects from 16 to 75 years of age, both inclusive. Subjects under 18 years of age may have been included only where permitted legally and ethically accepted. In Germany, only subjects 18 years and older may have been included.
- Subjects with well-characterized POS according to the International League Against Epilepsy (ILAE) classification (1981) or focal epilepsy or epileptic syndrome according to the ILAE classification (1989).
- Subjects with a history of inadequately controlled POS that may have been classified as simple or complex, whether or not secondarily generalized (Type I seizures according to the ILAE 1981 classification).
- Subjects having had at least 2 but not exceeding 40 POS, whether or not secondarily generalized, per 4 weeks during the 8-week Baseline Period.
- Subjects on a stable dose of at least 1, but no more than 2, Baseline AEDs for at least 4 weeks before Baseline (Visit 1), and who were expected to remain on a stable dose until the Baseline AED Tapering Period commenced. If a second AED was taken, its dose had to be ≤50% of the minimum recommended maintenance dose approved in the US for at least 4 weeks before Baseline (Visit 1).

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 (BX1000685), BRV 25mg (BX1000700, BX1000703)

Duration of treatment: The total duration of the study was up to 31 weeks by subject with a maximum exposure to BRV of 21weeks: Baseline Period (8 weeks), Treatment Period (17 weeks comprised of 1-week BRV Add-On Period, 8-week Baseline AED Tapering Phase, and 8-week Monotherapy Phase), Reconversion Period (3 to 4 weeks), and study

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drug-free Follow-Up Period (2 weeks).

Reference therapy, dose(s) and mode of administration, batch number(s): Matching placebo (PBO) was supplied as white, [redacted] tablets, 10mg and 25mg. Batch numbers: PBO 10mg (16088), 25mg (BX1000635)

Criteria for evaluation:

Efficacy: The primary efficacy variable was the cumulative exit rate at 112 days after the beginning of the Baseline AED Tapering Phase. Subjects were defined as having met an exit criterion if they met at least 1 of the 4 exit criteria during the Evaluation Period (Baseline AED Tapering Phase and Monotherapy Phase).

Sensitivity analyses for the primary efficacy variable were performed to evaluate the impact of premature discontinuations and protocol deviations on the assessment of primary efficacy.

Exploratory efficacy variables included the following: QOLIE-31-P, HADS scores, EQ-5D items, P-GES, I-GES, direct cost parameters (concomitant medications, medical procedures, healthcare provider consultations not foreseen by the protocol, and hospitalizations), indirect cost parameters (number of working or school days lost by the subject and/or caregiver and days with caregiver's help), and socio-professional data.

Pharmacokinetics/pharmacodynamics: The pharmacokinetic variables included the following: BRV (parent compound only) plasma levels and concomitant AED (and/or relevant metabolites) plasma levels.

Safety: The safety variables included the following: adverse event (AE) reporting; clinical laboratory tests (blood chemistry, hematology, and urinalysis); electrocardiogram (ECG); physical and neurological examinations; vital signs (including orthostatic measurements); and body weight.

Statistical methods: The primary efficacy analysis was the cumulative exit rate at 112 days after the beginning of the Baseline AED Tapering Phase. Subjects were defined as having met an exit criterion if they met at least 1 of the 4 exit criteria during the Evaluation Period.

The time of the exit was the earliest date an exit criterion was met. Subjects who did not meet any exit criteria were censored at Day 112 or at the date of last BRV dose in the Evaluation Period. Subjects who prematurely discontinued the study during the Evaluation Period due to reasons unrelated to exit criteria were censored as of the last dose of BRV during the Evaluation Period. A subject who had been erroneously exited by the Investigator based on Exit Criterion 1 or 2, but not actually having reached these criteria

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according to the statistical analysis (this may have happened in case of data entry errors of seizure count in the electronic data capture system) was considered censored for these analyses if the Investigator confirmed that no other exit criterion had been met by the subject.

Kaplan-Meier methods were used to estimate the cumulative exit rate (Allison 1995). The primary comparison was BRV 50mg/day versus historical control, where the historical control was based upon estimates of the exit rate obtained from the White Paper on Alternative Monotherapy Design in the Treatment of Epilepsy (French et al, 2009). Specifically, the cumulative rate of subjects who had exited the study at 16 weeks or 112 days after the beginning of the Baseline AED Tapering Period was compared to the historical lower bound estimate of the 80% prediction interval (computed assuming a sample size of 50 subjects) of the cumulative rate of subjects who had exited the study. This lower bound historical estimate was computed to be 0.722 (French et al, 2009).

The primary hypothesis was as follows:

- Null hypothesis:
  H_0: 1 - S(t)=0.722
- Alternative hypothesis:
  H_A: 1 - S(t) <0.722, where S(t) was the cumulative rate of subjects remaining in the study 112 days after the beginning of the Baseline AED Tapering Phase, and was also known as the survivorship function or cumulative survival rate.

The hypothesis was assessed using confidence interval (CI) estimates. If the upper 2-sided 95% limit from the Kaplan-Meier estimate of the percent exiting at 112 days after the beginning of the Baseline AED Tapering Phase for the BRV 50mg/day treatment group was less than 0.722, then the null hypothesis would have been rejected in favor of the alternative. This was analogous to a 1-sided test with a Type I error rate of 0.025. Inferential evaluation of the primary efficacy endpoint was to be conducted for the BRV 50mg/day dose group.

Sensitivity analyses for the primary efficacy variable were performed to evaluate the impact of premature discontinuations and protocol deviations on the assessment of primary efficacy.

Summary and conclusions: After approximately one-half of the originally planned subjects had been enrolled in N01276, ongoing monitoring of both N01276 and the identically designed sister study, N01306, suggested a higher than expected number of subjects discontinuing either for predefined exit criteria or other reasons. As a result, UCB

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decided to amend both protocols to allow for an interim analysis and implemented a temporary recruitment hold until after the interim analysis. The main objective of the interim analysis was to gain an understanding of the reasons for the higher than expected discontinuation rate and to evaluate futility relative to the assessment of primary efficacy for the BRV 50mg/day arm. The interim analysis included data from the individual studies as well as pooled data from the 2 sister studies. The data from the interim analysis were referred to an Independent Data Monitoring Committee (IDMC) for a review of unblinded data presentations. The IDMC noted that at least 1 or more of the predefined criteria for stopping the studies were met, but in order to preserve the blind, did not specify the futility criteria that were met. The IDMC confirmed that they did not detect any safety concerns in the data review. The UCB study team remained blinded throughout the interim analysis, as well as to the unblinded discussion summary and the findings of the IDMC until after the database lock for both studies.

As a result of the interim analysis and recommendation by the IDMC, UCB decided to stop both N01276 and N01306 due to futility and a predicted low probability of success for both studies at the final analysis. At the time N01276 was stopped, 88 of the 178 initially planned subjects (updated to 238 subjects based on a revised historical control exit rate) for N01276 had been randomized

Due to the premature termination of N01276 and resulting limited sample size, the planned statistical comparison of data obtained in N01276 with historical-control data is not feasible. Due to the small sample size for calculation of the 95% CI for the Kaplan-Meier estimate of exit rate at Day 112, CIs for the primary efficacy variable and the related sensitivity analyses for the BRV 50mg/day group should be interpreted with caution. The 3:1 randomization (BRV 50mg/day:BRV 100mg/day) of subjects imposes additional limitations to the planned descriptive evaluation of the BRV 100mg/day group.

Subject disposition: Of the 164 subjects enrolled in the study, 76 subjects (46.3%) were screen failures. The reasons for screen failure were ineligibility based on inclusion/exclusion criteria (53 subjects), withdrawal of consent not related to AEs (8 subjects), lost to follow-up (1 subject), and other reasons (13 subjects). For 1 subject, the reason for screen failure was not known.

The Intent-to-Treat (ITT) Set was comprised of 88 subjects who were randomized to treatment (68 to BRV 50mg/day and 20 to BRV 100mg/day). Eighty-seven subjects were randomized, treated, entered the Evaluation Period, and were included in the Efficacy (EFF) Set. The ITT Set, which was comprised of the same subjects as the Safety Population, was used for safety analysis.

Of the 88 subjects in the ITT Set, 31 subjects (35.2%) completed through the end of the

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Monotherapy Phase. Eighty-seven subjects (98.9%) completed the BRV Add-On Period, 56 subjects (63.6%) completed the Baseline AED Tapering Phase, and 31 subjects (35.2%) completed the Monotherapy Phase. The most common reason for discontinuation before the end of the Evaluation Period was lack of efficacy (13 subjects [14.8%] during the Baseline AED Tapering Phase and 16 subjects [18.2%] during the Monotherapy Phase).

Efficacy results: The small number of subjects enrolled in N01276 due to its premature termination prevents statistical comparison of data obtained in N01276 with historical control data. Due to the small sample size for calculation of the 95% CI for the Kaplan-Meier estimate of the exit rate at Day 112, these data should be interpreted with caution.

For the primary efficacy analysis, 26 subjects (38.8%) in the BRV 50mg/day group of the EFF Set met 1 or more exit criteria, with the mean time to the first occurrence of an exit event of 42.3 days (SD=21.6 days). The Kaplan Meier estimate of the exit rate at Day 112 was 0.487, with the upper limit of the 2-sided 95% CI (0.626) for this estimate was lower than the historical control exit rate (0.722).

Key sensitivity analyses were performed to limit the censoring in N01276 to that of the historical control population. For both key sensitivity analyses of the BRV 50mg/day group of the EFF Set, the upper limit of the 2 sided 95% CI for the Kaplan Meier estimate was greater than that of the historical control (0.722):

- For the analysis in which a maximum of 10% of subjects (first 10%) were censored, the Kaplan Meier estimate of the exit rate at Day 112 was 0.652 (95% CI: 0.532, 0.772).
- For the analysis in which a maximum of 10% of subjects (randomly selected) were censored, the Kaplan Meier estimate of the exit rate at Day 112 was 0.627 (95% CI: 0.507, 0.748).

For the additional sensitivity analyses of the BRV 50mg/day group of the EFF Set, the upper limit of the 2 sided 95% CI for the Kaplan Meier estimate was less than that of the historical control (0.722) for 1 of the 3 analyses:

- For the analysis for which subjects who discontinued the Evaluation Period due to an AE or lack of efficacy were considered as having met exit criteria, the Kaplan Meier estimate of the exit rate at Day 112 was 0.529 (95% CI: 0.392, 0.666).
- For the analysis for which any dropouts during the Evaluation Period were considered as having met exit criteria, the Kaplan Meier estimate of the exit rate at Day 112 was 0.657 (95% CI: 0.540, 0.773).

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- For the analysis in which all subjects censored before Day 112 of the Evaluation Period were considered as having met exit criteria the Kaplan Meier estimate of the exit rate at Day 112 was 0.687 (95% CI: 0.575, 0.798).

Pharmacokinetics/pharmacodynamics results: Meaningful interpretation of data pertaining to mean plasma concentrations of BRV is limited due to small sample size.

Safety results: Sixty-three subjects (71.6%) in the ITT Set experienced treatment-emergent adverse events (TEAEs) during the Treatment Period. Most TEAEs were considered mild or moderate in intensity by the Investigator, and none resulted in death. Those TEAEs experienced by at least 5% of all subjects in the ITT Set during the Treatment Period were headache and anxiety (each in 8 subjects, 9.1%); fatigue, decreased appetite, convulsion, and depression (each in 7 subjects, 8.0%); and nausea, nasopharyngitis, and insomnia (each in 5 subjects, 5.7%).

Forty-two subjects (47.7%) in the ITT Set experienced TEAEs during the Treatment Period considered study drug-related by the Investigator. Of these TEAEs, those experienced by at least 5% of subjects were fatigue (7 subjects, 8.0%); convulsion (6 subjects, 6.8%); and decreased appetite and anxiety (each in 5 subjects, 5.7%).

Eleven subjects (12.5%) in the ITT Set experienced TEAEs leading to discontinuation from the Treatment Period. For 8 of these subjects, the TEAEs were associated with epilepsy (convulsion in 5 subjects, grand mal convulsion in 2 subjects, and status epilepticus in 1 subject) and met the criteria for exit. One additional subject had a primary reason for discontinuation from the Evaluation Period of "adverse event," but none of the TEAEs reported for this subject had "study medication withdrawn" as the action taken. This subject met a predefined exit criterion and the event leading to exit was reported as a TEAE.

Five subjects (5.7%) in the ITT Set experienced treatment-emergent serious adverse events (SAEs) during the Treatment Period. For 4 subjects (4.5%), the SAEs were considered possibly related to study drug by the Investigator. These included grand mal convulsion; grand mal convulsion/loss of consciousness; status epilepticus; and dizziness/paraesthesia/anxiety (each in 1 subject). All SAEs resolved.

For all clinical laboratory parameters evaluated, mean changes from Baseline to last visit in the Treatment Period were generally small and not clinically relevant. Three subjects in the ITT Set had treatment-emergent possibly clinically significant (PCS) values in hematology parameters and 14 subjects in the ITT Set had treatment-emergent PCS values in clinical chemistry parameters during the Treatment Period. Urinalysis findings were negative for the majority of subjects in the ITT Set.

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Treatment-emergent PCS values for weight during the Treatment Period were recorded in the database for 9 subjects. Three subjects in the ITT Set had treatment-emergent PCS values for vital signs during the Treatment Period; none of these values were reported as TEAEs.

Normal ECGs were maintained from Baseline to Visit 4 and from Baseline to the last visit in the Treatment Period for the majority of subjects. Nine subjects (10.8%) had normal ECGs at Baseline that were abnormal at the last visit in the Treatment Period; these changes were not clinically significant and were not reported as TEAEs.

Conclusions: Conclusions regarding the efficacy of BRV for use as conversion to monotherapy in subjects with uncontrolled POS were not possible due to the premature termination of the study and confounding effects of dropouts.

A higher than expected rate of premature discontinuations was a critical factor in the decision to stop the study; however, no particular trend or pattern in premature discontinuations was observed.

In this historical-control, conversion to monotherapy study, BRV at doses of 50mg/day and 100mg/day was generally well tolerated in subjects from 17 to 69 years old with POS, and no unexpected safety concerns were identified.

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