CLINICAL STUDY REPORT SYNOPSIS: N01254

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Title of study: An international, randomized, double-blind, parallel-group, placebo-controlled, flexible dose study: evaluation of the safety and efficacy of brivaracetam in subjects (≥16 to 70 years old) suffering from localization-related or generalized epilepsy

Investigator(s): 74 Investigators screened subjects for this study

Study site(s): Multicenter study conducted in 15 countries (Austria, Belgium, Czech Republic, Germany, Hong Kong, India, Italy, South Korea, Norway, South Africa, Russia, Singapore, Sweden, Taiwan, and Ukraine); 74 sites screened at least 1 subject and 74 sites randomized at least 1 subject.

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

Studied period: 25 weeks **First subject enrolled:** 15 Oct 2007 **Last subject completed:** 15 Dec 2008	**Phase of development:** Phase 3

Objective(s): The primary objective of the study was to assess the safety and tolerability of brivaracetam (BRV) at the dose range from 20 to 150mg/day in twice daily administration in subjects suffering from localization-related or generalized epilepsy not fully controlled despite optimal treatment with 1 to 3 concomitant antiepileptic drug(s) (AED[s]), compared to placebo (PBO).

Secondary objectives of the study were:

- To confirm the efficacy of BRV in reducing partial-onset seizure (POS; Type I) frequency in subjects suffering from localization-related epilepsy
- To assess the effects of BRV on different dimensions of subjects' functioning and Health Related Quality of Life (HRQoL) in subjects suffering from localization-related epilepsy
- To assess the effects of BRV on Type IC seizures

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Exploratory objectives of the study were:

- To explore the efficacy of BRV in reducing Type II seizure days in subjects suffering from generalized epilepsy
- To explore the effects of BRV on subjects' HRQoL in subjects suffering from generalized epilepsy
- To obtain a description of the subject's self-reported health status
- To explore direct medical resource use and indirect cost parameters
- To collect blood samples for genotyping of SV2-and epilepsy-related genes (for a pooled analysis at the program level)

Methodology: This was a 19-week, Phase 3, randomized, double-blind, parallel-group, placebo-controlled, flexible-dose study conducted to determine the safety and tolerability of BRV in subjects with localization-related or generalized epilepsy. A secondary objective was to confirm the efficacy of BRV in reducing POS frequency in subjects suffering from localization-related epilepsy. An exploratory objective was to evaluate the efficacy of BRV in reducing Type II seizure frequency in subjects suffering from generalized epilepsy.

Subjects were enrolled and entered a 4-week Baseline Period. At the end of the Baseline Period, subjects were centrally randomized (3:1 in random permuted blocks) to 1 of 2 treatment arms (BRV 20mg/day or matching PBO) and entered an 8-week Dose-Finding Period. During the Dose-Finding Period, subjects either remained at the BRV 20mg/day dose or were uptitrated to either BRV 50mg/day, BRV 100mg/day, or BRV 150mg/day in a stepwise manner. Oral tablets of BRV (10mg and 25mg) and matching PBO were used in the study. One fallback option was offered at doses ≥50mg/day. Subjects entered an 8-week Maintenance Period at the last dose reached in the Dose-Finding Period. The daily dose was administered in 2 equal intakes, morning and evening. After completion of the Maintenance Period, subjects either entered a long-term follow-up (LTFU) study or entered a Down-Titration Period of up to 3 weeks followed by a 2-week Study Drug-Free Period. Subjects who entered the LTFU study either remained at the same dose, or if receiving BRV 150mg/day, were down-titrated to BRV 100mg/day. For subjects not entering the LTFU study and taking doses of BRV 50mg/day, 100mg/day, or 150mg/day (or corresponding matching PBO), a Down-Titration Period of 1, 2, or 3 weeks, respectively, was required prior to entering the Study Drug-Free Period.

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Number of subjects (planned and analyzed): 470 randomized subjects were planned (with no more than 20% of subjects with generalized epilepsy); a total of 543 subjects were screened and 480 subjects were randomized (431 subjects [89.8%] with POS and 49 subjects [10.2%] with primarily generalized seizures [PGS]).

Diagnosis and main criteria for inclusion:

1. Subjects were aged from 16 to 70 years, inclusive. Subjects under 18 years of age were only included where legally permitted and ethically accepted.
2. Subjects had well-characterized localization-related epilepsy or generalized epilepsy according to the International League Against Epilepsy (ILAE) classification
3. For subjects suffering from localization-related epilepsy:
   - Subjects had at least 2 POSs whether or not secondarily generalized per month during the 3 months preceding Visit 1 according to the ILAE classification
   - Subjects had at least 4 POSs whether or not secondarily generalized during the 4-week Baseline Period according to the ILAE classification
4. For subjects suffering from generalized epilepsy:
   - Subjects had at least 2 Type II-seizure days per month during the 3 months preceding Visit 1 according to the ILAE classification
   - Subjects had at least 4 Type II-seizure days during the 4 week Baseline Period according to the ILAE classification
5. Subjects were uncontrolled while treated by 1 to 3 permitted concomitant AED(s). Vagal nerve stimulation was allowed and was not counted as a concomitant AED.

Main criteria for exclusion:

1. For subjects who suffered from localization-related epilepsy: history or presence of seizures occurring only in clusters (too frequently or indistinctly separated to be reliably counted) before Visit 2 or occurring only as Type IA nonmotor
2. Subjects with a 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 of 10mg (batch numbers: 15528, 15800, 15801, BX1000685) and 25mg (batch numbers: 14916, 15216, 15451, 15525).

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	
Duration of treatment: The total duration of the study was up to 25 weeks by subject, with a maximum 19-week exposure to BRV: Baseline Period (4 weeks), Treatment Period (Dose-Finding Period [8 weeks] + Maintenance Period [8 weeks]), Down-Titration Period (up to 3 weeks), and 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 of 10mg (batch numbers: 15529, 15802, 15944, 16085) and 25mg (batch numbers: 15069, 15943, BX1000635).		
Criteria for evaluation: The primary objective of this study was to determine the safety and tolerability of BRV in subjects with POS or PGS. Analyses of efficacy were secondary and/or exploratory objectives.		

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Efficacy:

The primary efficacy variable was the POS (Type I) frequency per week over the Treatment Period (Dose-Finding Period + Maintenance Period) in subjects suffering from localization-related epilepsy.

In subjects suffering with localization-related epilepsy, the secondary efficacy variables included:

- Responder rate for POS (Type I) over the Treatment Period (ie, the proportion of subjects who had a ≥50% reduction in POS [Type I] frequency per week from Baseline)
- Seizure frequency per week (all seizure types) over the Treatment Period
- Percent reduction for POS (Type I) frequency per week from Baseline Period to the Treatment Period
- Categorized response for POS (Type I) over the Treatment Period. (ie, percent reduction in POS [Type I] frequency per week from Baseline of <-25%, -25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%)
- Seizure freedom rates for all seizure types over the Treatment Period
- Reduction of Type IC/Type I seizure frequency ratio from Baseline to the Treatment Period
- Time to nth (n=1, 5, 10) Type I seizure during the Treatment Period
- Total score on the Patient Weighted Quality of Life in Epilepsy Inventory-Form 31 (QOLIE-31-P)
- Seizure Worry score on the QOLIE-31-P
- Daily Activities/Social Functioning score on the QOLIE-31-P
- Remaining domain scores on the QOLIE-31-P (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)

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Exploratory efficacy variables for subjects with PGS included:

- Generalized seizure (Type II) days per week over the Treatment Period
- Seizure days per week for each seizure subtype over the Treatment Period
- QOLIE-31-P dimensions (Seizure Worry, Daily Activities/Social Functioning, Energy/Fatigue, Emotional Well-being, Cognitive Functioning, Overall Quality of Life, Medication Effects) and Total score
- HADS scores (Anxiety, Depression)
- P-GES
- I-GES
- Seizure days per week (all seizure types) over the Treatment Period
- Percent reduction for generalized seizure (Type II) days per week from Baseline Period to the Treatment Period
- Responder rate for generalized seizures (Type II) over the Treatment Period (ie, the proportion of subjects who had a ≥50% reduction in generalized seizure [Type II] days per week from Baseline)
- Categorized response for the generalized seizures (Type II) over the Treatment Period (ie, percent reduction in generalized seizure [Type II] days per week from Baseline of <25%, 25% to <25%, 25% to <50%, 50% to <75%, 75% to <100%, and 100%)
- Seizure freedom rates for all seizure types over the Treatment Period
- Time to n^{th} (n=1, 5, 10) Type II seizure day during the Treatment Period

Additional exploratory variables included for the Intent-to-Treat (ITT) Population (POS, PGS, and overall ITT):

- EuroQoL-5 dimensions 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)

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

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
- Laboratory tests (including blood chemistry, hematology, and urinalysis)
- Vital signs (including orthostatic measurements)
- Physical and neurological examinations
- Psychiatric and mental status
- Electrocardiograms (ECG)
- Body weight and height

Statistical methods: The primary efficacy variable was the POS (Type I) frequency per week over the Treatment Period. It was calculated for each subject 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, study region, and concomitant levetiracetam (LEV) use (as recorded in the case report form) as factors and the log-transformed Baseline seizure frequency per week as covarite. This analysis was repeated for the Dose-Finding and Maintenance Periods; however, these analyses were considered secondary to the primary efficacy analysis over the Treatment Period.

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Summary and conclusions:

Subject disposition: A total of 543 subjects were screened and 63 of these subjects were screen failures. The most common reasons for screen failure were ineligibility (49 of 63 subjects) and withdrawal of consent for personal reasons (not related to AEs) (8 of 63 subjects). The remaining 480 subjects were randomized 3:1 to BRV (n=359) or PBO (n=121) and were included in the ITT Population. The Safety Population was comprised of the same set of subjects as the ITT Population. Of the 480 subjects in the ITT Population, 434 subjects (90.4%) completed the study; completion rates were similar between treatment groups. Of the subjects who completed the study, 417 subjects (86.9%) completed the Treatment Period and entered the LTFU, and 17 subjects (3.5%) completed the Treatment Period and did not enter the LTFU, but completed the Down-Titration Period and Safety Follow-Up Visit. A total of 46 subjects (9.6%) discontinued the study, 10 subjects (8.3%) in the PBO group and 36 subjects (10.0%) in the BRV group. The most common reason for discontinuation was AE for both treatment groups (7 subjects [5.8%] in the PBO group and 23 subjects [6.4%] in the BRV group).

The disposition of subjects with POS was similar to the overall ITT population. A total of 431 subjects with POS (108 in the PBO group and 323 in the BRV group) were included in the study. Of the 431 subjects in the ITT POS Population, 388 subjects (90.0%) completed the study; completion rates were similar between treatment groups. Of the subjects who completed the study, 372 subjects (86.3%) completed the Treatment Period and entered the LTFU, and 16 subjects (3.7%) completed the Treatment Period and did not enter the LTFU, but completed the Down-Titration Period and Safety Follow-Up Visit. A total of 43 subjects with POS (10.0%) discontinued the study, 10 subjects (9.3%) in the PBO group and 33 subjects (10.2%) in the BRV group. The most common reason for discontinuation was AE for both treatment groups (7 subjects [6.5%] in the PBO group and 22 subjects [6.8%] in the BRV group).

A total of 49 subjects with PGS (13 in the PBO group and 36 in the BRV group) were included in the study. Of the 49 subjects in the ITT PGS Population, 46 subjects (93.9%) completed the study; all 13 subjects in the PBO group and 33 of 36 subjects (91.7%) in the BRV group completed the study. Of the 3 subjects in the BRV group who did not complete the study, 1 withdrew due to an AE, 1 was lost to follow-up, and 1 withdrew for "other" reasons.

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Efficacy results: The primary efficacy variable was the POS frequency per week over the Treatment Period. The percent reduction over PBO in the POS frequency per week over the Treatment Period was 7.3%. This primary efficacy outcome for this study did not achieve statistical significance at the 0.050 level (p=0.125). Results for a Linear Mixed-Effects Model including terms for treatment, week, treatment-by-week interaction, subject, and stratification factors, and log-transformed Baseline seizure frequency per week as a continuous covariate were consistent with the primary ANCOVA. Additional sensitivity analyses (rank-ANCOVA and primary ANCOVA analysis on PP Population) were also consistent with the primary ANCOVA analysis.

In contrast to the primary efficacy endpoint, the 50% responder rate over the Treatment Period was statistically significantly different (p=0.006) for BRV (30.3%) compared with PBO (16.7%). For the categorized response rate in POS frequency per week over the treatment period, the BRV group was statistically significantly different compared with the PBO group (p=0.036) during the Treatment Period. The remaining secondary endpoints were consistent with the primary efficacy endpoint. Additionally, 5 subjects receiving BRV were seizure free for the entire Treatment Period compared to 0 subjects receiving PBO.

For subjects with PGS, the median number of seizure days per week decreased from a median of approximately 1.5 days for both treatment groups during the Baseline Period to a median of 0.63 days for the BRV group and 1.26 days for the PBO group during the Treatment Period. The 50% responder rate for subjects with PGS during the Treatment Period was 15.4% (2 of 13 subjects) for the PBO group and 44.4% (16 of 36 subjects) for the BRV group. The median percent reduction from Baseline in PGS days per week over the Treatment Period was higher in the BRV group (42.57%) than the PBO group (20.74%). Two of 36 subjects receiving BRV and 0 of 13 subjects receiving PBO were seizure free during the entire Treatment Period.

There were no meaningful differences in health-related quality of life or indirect or direct cost parameters between the BRV and PBO groups for the POS or PGS Populations.

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

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Safety results: The incidence of treatment-emergent AEs (TEAEs) during the Treatment Period was similar in the BRV group (66.0%) compared with the PBO group (65.3%) for the overall Safety Population. For the POS Safety Population, the incidence of TEAEs during the Treatment Period was similar to the overall Safety Population (65.3% for the BRV group and 63.9% for the PBO group). For the PGS Safety Population, the incidence of TEAEs during the Treatment Period was similar in the BRV group (72.2%, 26 of 36 subjects) and PBO group (76.9%, 10 of 13 subjects). For the overall Safety Population, the most common TEAEs during the Treatment Period for the BRV group compared with the PBO group were as follows: headache (14.2% vs 19.8%), somnolence (11.1% vs 4.1%), dizziness (8.6% vs 5.8%), fatigue (7.8% vs 4.1%), nausea (5.6% vs 8.3%), convulsion (5.0% vs 3.3%), nasopharyngitis (3.9% vs 6.6%), and back pain (3.1% vs 6.6%). These TEAEs were also the most common TEAEs during the Treatment Period for the POS Safety Population, and were among the most common TEAEs during the Treatment Period for the PGS Safety Population.

The majority of TEAEs reported during the Treatment Period for the overall Safety Population were mild or moderate in intensity; the percentage of subjects with severe TEAEs was 6.7% for the BRV group and 5.8% for the PBO group. During the Treatment Period, the incidence of drug-related TEAEs (per the Investigator) was higher in the BRV group (40.7%) than in the PBO group (32.2%) for the overall Safety Population. The most frequently reported drug-related TEAEs for the BRV group compared with the PBO group were as follows: somnolence (10.0% vs 3.3%), headache (7.0% vs 7.4%), and fatigue (6.7% vs 4.1%). For the overall Safety Population, the incidence of TEAEs that led to permanent study drug discontinuation during the Overall Period was 6.4% in the BRV group and 5.0% in the PBO group. Treatment-emergent AEs that led to permanent study drug discontinuation were most frequently reported in the nervous system disorders system organ class (SOC); the most frequently reported preferred term was convulsion (1 subject in the PBO group and 4 subjects in the BRV group).

The incidence of serious AEs for the overall Safety Population during the Overall Period was 7.4% in the PBO group and 5.6% in the BRV group. One subject died during the study. This subject was a [redacted] who drowned 62 days after first study-drug intake while receiving BRV 50mg/day; this SAE was considered unlikely related to study drug by the Investigator.

For the overall Safety Population, the incidence of TEAEs during the Treatment Period in subjects with concomitant LEV use was 73.5% in the BRV group and 78.3% in the PBO group and was 64.3% in the BRV group and 62.2% in the PBO group in subjects without concomitant LEV use.

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Several UCB SOCs and UCB grouping terms of special interest were evaluated during this study. In general, there were no clinically meaningful differences between groups 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).

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 clinically 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 possibly clinically significant (PCS) hematology and blood chemistry values was low and similar between treatment groups during the Treatment Period.

The incidence of PCS urine values was generally similar between treatment groups during the Treatment Period, with the exception of higher incidences in the BRV group compared with the PBO group for: blood urine (15.2% vs 10.7%, respectively), urine leukocyte esterase (10.4% vs 5.0%, respectively), protein urine (3.9% vs 0%, respectively), WBC urine (sediment) (13.8% vs 9.1%, respectively), monohydrate calcium oxalate crystals (1.7% vs 0%, respectively), and dihydrate calcium oxalate crystals (10.6% vs 5.8%, respectively). The incidence of AEs in the UCB grouping term of urinary tract infections was similar between the treatment groups (1.7% [2 subjects] in the PBO group and 1.7% [6 subjects] in the BRV group).

There were no clinically meaningful changes in vital sign parameters. Few TEAEs were associated with PCS vital sign values.

The majority of subjects in both treatment groups who had ECG abnormalities at Baseline or at the last visit on treatment had abnormalities that were considered not clinically significant.

There were no clinically meaningful differences in physical or neurological examination findings, in psychiatric or mental status, or in the number of concurrent medical procedures during this study between treatment groups.

Name of company: UCB Pharma SA	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product:	**Volume:**	
Name of active ingredient: Brivaracetam	**Page:**	

Conclusions:

- Brivaracetam was generally well tolerated. The incidence of TEAEs during the Treatment Period was similar between treatment groups for the overall Safety Population, the POS Safety Population, and the PGS Safety Population. The most common TEAEs during the Treatment Period for the BRV group for the overall Safety Population were headache, somnolence, dizziness, fatigue, nausea, convulsion, nasopharyngitis, and back pain; the TEAEs of somnolence and fatigue were the only TEAEs that occurred at a ≥3% higher incidence in the BRV group compared with the PBO group.
- The majority of TEAEs reported during the Treatment Period for the overall Safety Population were mild or moderate in intensity; the percentage of subjects with severe TEAEs was similar between treatment groups. For the overall Safety Population, the incidence of TEAEs that led to permanent study drug discontinuation during the Overall Period was 6.4% in the BRV group and 5.0% in the PBO group. The incidence of SAEs for the overall Safety Population during the Overall Period was 7.4% in the PBO group and 5.6% in the BRV group.
- The percent reduction over PBO in the POS frequency per week over the Treatment Period was 7.3%. This primary efficacy outcome for this study did not achieve statistical significance.
- In contrast to the primary efficacy endpoint (POS Population), the 50% responder rate over the Treatment Period was statistically significantly different (p=0.006) for BRV (30.3%) compared with PBO (16.7%). Five subjects receiving BRV were seizure free for the entire Treatment Period compared to 0 subjects receiving PBO.
- Because of the small sample size of the PGS population, no definite efficacy conclusions can be drawn for these subjects; however, the results support the further evaluation of BRV for the treatment of generalized epilepsy.

Report date: 06 Jul 2010