DEV/EDV/05239.2006

1. SYNOPSIS

Name of Sponsor/Company: UCB S.A. Belgium	Individual Study Table Referring to Module 5.3.5	*(For National Authority Use only)*
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Title of Study: A multicenter, double-blind, randomized, placebo-controlled, 4 parallel groups, dose-ranging trial evaluating the efficacy and safety of brivaracetam used as adjunctive treatment at doses of 5, 20 and 50 mg/day in b.i.d. administration (oral tablets of 2.5 or 10 mg) for a maximum of 7 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized.

Investigator(s) / Study Center(s): Forty-one centers in Brazil, India, Mexico and the United States actively participated (enrolled at least one subject) in this study.

Publication: None at the time of this report.

Studied Period (years): **First Subject First Visit:** 07-Nov-2005 **Last Subject Last Visit:** 29-Jun-2006	**Phase of Development:** Phase II / Therapeutic exploratory

Objectives:
Primary Objective: To evaluate the efficacy of brivaracetam at the doses of 5, 20 and 50 mg/day in *b.i.d.* administration in reducing seizure frequency in subjects with partial onset seizures not fully controlled despite treatment with 1 or 2 concomitant antiepileptic drugs (AEDs).
Secondary Objectives: To evaluate the dose/clinical response relationship and narrow down the dose range of clinical interest, explore tolerability of brivaracetam in the same population, to collect data on seizure-free days and seizure-free subjects and to bridge the results on efficacy and safety with N01114 study.
Exploratory Objectives: To explore the population pharmacokinetics of brivaracetam and identify relevant covariates, and to assess the impact of brivaracetam on concomitant AED plasma levels.

Methodology:
This trial was designed as a double-blind, randomized, placebo-controlled, multicenter, 4-parallel groups, dose ranging study.

Number of Subjects:
It was foreseen to randomize 204 (51 per group) subjects. A total of 256 subjects were screened, 210 subjects were randomized.

Diagnosis and Main Criteria for Inclusion:
Male/female subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized.

Test Product: Brivaracetam (2.5 and 10 mg tablet)	**Dose and Mode of Administration:** 5, 20 and 50 mg *b.i.d.* (oral administration)	**Batch Number:** 14333, 14329, 14206

Duration of Treatment:
The total duration of the trial per subject was up to 13 weeks (3 months) with a limitation to 7 week exposure to brivaracetam (BRV) without any up-titration or down-titration period.

Reference Therapy: Matching Placebo (tablet)	**Dose and Mode of Administration:** 5, 20 and 50 mg *b.i.d.* (oral administration)	**Batch Number:** 14330, 14204

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Criteria for Evaluation:

Efficacy:

Primary Efficacy:

The primary efficacy endpoint was the partial onset seizure frequency per week during the treatment period.

Secondary Efficacy:

The secondary efficacy variables were as follows:

- Seizure frequency per week for all seizures (types I+II+III) over the Treatment Period.
- Reductions and percentage reductions from Baseline in seizure frequency per week for partial onset seizures (type I) and for all seizures (types I+II+III) over the Treatment Period.
- Responder rate in partial onset seizures (type I) over the Treatment Period. A responder is defined as a subject with a $\geq$ 50% reduction in seizure frequency per week from the Baseline Period to the Treatment Period.
- Response to treatment in partial onset seizures (type I) over the Treatment Period. The percentage reduction from Baseline in partial seizure frequency per week over the Treatment Period grouped in 5 categories: < -25%, -25% to < 25%, 25% to < 75%, and 75% to < 100%, and 100%.
- Percentage of seizure-free subjects over the Treatment Period.
- Percentage of seizure-free days per 4 weeks over Baseline and Treatment Periods.
- Time to N-th seizure in the Treatment Period.

Exploratory Efficacy:

The exploratory efficacy variables were as follows:

- Patient's Global Evaluation Scale at the Evaluation Visit or Early Discontinuation Visit.
- Investigator's Global Evaluation Scale at Evaluation Visit or Early Discontinuation Visit.

Pharmacokinetics:

Pharmacokinetic (PK) variables were based on the following parameters:

- Brivaracetam (parent compound only) plasma level determined at each specified visit under trial drug.
- Concomitant AEDs (and/or relevant metabolites) plasma levels determined in all subjects at baseline (Visit 1, Visit 2), at each specified visit under trial drug and during the Trial Drug-free Period (Safety Visit).

Safety:

Safety variables were based on the following parameters:

- Adverse events reporting.
- Laboratory tests (including blood and urine).
- Electrocardiogram (ECG) measurements.
- Physical and neurological examinations.
- Vital signs including orthostatic hypotension.
- Body weight.

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Statistical Methods:

The null hypotheses of no treatment difference between each randomized dose of BRV versus placebo (PBO) were tested statistically on the partial onset seizure frequency per week, adjusted for two stratification variables and for baseline seizures. The trial would be considered positive if at least one of these null hypotheses was rejected in favor of BRV at the significance level of 5% (two-sided). Statistical hypothesis tests were two-sided at the 5% significance level, without adjustment for multiplicity.

Treatment groups were compared with respect to the log-transformed primary efficacy variable using an ANCOVA model. The model included as factors randomization group and strata (concomitant use of carbamazepine (yes/no) and the use of levetiracetam (no/prior/concomitant)), and as a covariate the log-transformed baseline partial onset seizure frequency per week. Differences in treatment LSMEANS between each randomized dose of BRV and PBO were expressed as a percentage reduction over PBO, with 95% confidence intervals (CIs).

Statistical methods used for other efficacy variables were: Wilcoxon-Mann-Whitney test and Hodges-Lehmann method (absolute and percentage reductions from baseline), logistic regression (responder rate), Cochran-Mantel-Haenszel test (categorized response to treatment), Fisher's exact test for numbers of seizure-free subjects, and Cox proportional hazards regression / Kaplan-Meier curves for times to 1st, 5th and 10th seizures.

Exploratory efficacy and safety variables were analyzed descriptively (by randomization group).

SUMMARY – CONCLUSIONS

EFFICACY RESULTS (primary and secondary variables):

Overall, of the 256 subjects screened, 210 were randomized and 208 subjects were included in the ITT population. Of the ITT subjects 196 were included in the per protocol analysis. A total of 154 subjects were exposed to BRV during the study. The primary efficacy analysis was performed on the ITT population during the treatment period.

The estimated percent reductions over PBO in the partial onset seizure frequency per week were 9.8%, 14.9% and 22.1% for BRV 5 mg, 20 mg and 50 mg, respectively, suggestive of a dose response (see Table below). The difference over PBO was statistically significant (p=0.004) for BRV 50 mg and approached statistical significance for BRV 20 mg (p=0.062). Therefore the study showed superiority of BRV 50 mg over PBO. The same conclusion also applied to the primary efficacy analysis performed on the PP population. Results for type I+II+III seizures were very similar to those for partial (type I) seizures.

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	PBO N=54	**BRV 5 N=50**	**BRV 20 N=52**	**BRV 50 N=52**
LS means (log-transformed)	1.296	1.194	1.135	1.047
LS means (back-transformed)	2.656	2.299	2.110	1.848
Difference vs PBO				
% Reduction over PBO		9.8%	14.9%	22.1%
95% CI		(-7.2% , 24.0%)	(-0.8% , 28.2%)	(7.6% , 34.3%)
p-value		0.240	0.062	0.004

ANCOVA model with treatment group and each stratification as factors, log-transformed baseline seizure frequency per week covariate.

The nonparametric estimates of median difference versus PBO in partial seizure frequency per week were -13.6, -22.5 and -28.7 for BRV 5 mg, 20 mg and 50 mg, respectively, shown in the following table.

	PBO N=54	**BRV 5 N=50**	**BRV 20 N=52**	**BRV 50 N=52**
Evaluable Subjects	54	50	52	52
Median (Q1 – Q3)	21.70 (-12.04 – 42.99)	29.91 (3.83 – 53.33)	42.56 (-0.44 – 67.92)	53.05 (19.56 – 69.33)
Median diff vs PBO		-13.57	-22.45	-28.74
95% CI		(-31.63 , 1.65)	(-39.47 , -4.70)	(-45.10 , -13.62)
p-value		0.086	0.014	< 0.001

p-value from the Wilcoxon-Mann-Whitney test, 95%CI from Hodges-Lehmann method.

These median reductions compared to PBO were statistically significant for BRV 20 mg (p=0.014) and BRV 50 mg (p<0.001), and approached statistical significance for 5 mg (p=0.086). These nonparametric findings are also in line with the primary efficacy parametric results above.

The responder rates during treatment were 32.0%, 44.2%, and 55.8% for the BRV 5 mg, 20 mg and 50 mg groups, respectively, compared with 16.7% for PBO, shown in the table below. The observed treatment odds ratios versus PBO were 2.66, 4.27, and 7.21 for BRV 5 mg, 20 mg and 50 mg, respectively, indicating the odds to respond in the 3 BRV groups were 2.66, 4.27 and 7.21 times those in the PBO group.

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	PBO N=54	**BRV 5 N=50**	**BRV 20 N=52**	**BRV 50 N=52**
Evaluable Subjects	54	50	52	52
Non-responders	45 (83.3%)	34 (68.0%)	29 (55.8%)	23 (44.2%)
Responders	9 (16.7%)	16 (32.0%)	23 (44.2%)	29 (55.8%)
Odds Ratio (BRV vs PBO)		2.66	4.27	7.21
95% sided CI		(1.01, 6.96)	(1.68 , 10.84)	(2.80, 18.58)
p-value		0.047	0.002	< 0.001

Logistic regression modelling probability of being a responder with treatment group and stratification as factors and baseline seizure frequency as covariate.

These odds ratios were statistically significant at the 5% level (p=0.047, p=0.002, p<0.001) for BRV 5 mg, 20 mg and 50 mg, respectively. This is a similar finding to those for model-based primary efficacy and non-parametrically analyzed percent seizure reduction.

Four subjects completing the study were seizure-free on each of BRV 5 mg, 20 mg and 50 mg, compared to one subject completing and seizure-free on PBO.

The times to N-th seizure were similar for PBO and BRV 5 mg and BRV 20 mg. For BRV 50 mg vs PBO, the hazard ratios (ratios of the probabilities of instantaneous N-th seizure) were significantly less than one for 1st (p=0.044), 5th (p=0.023) and 10th seizure (p=0.023); this was reflected in greater median times to N-th seizure for BRV 50 mg.

SAFETY RESULTS:

Of the 208 subjects in the ITT population 11 (5.3%) discontinued, and 197 (94.7%) completed the study. Reasons for discontinuation were adverse events (7, 3.4%), lost to follow-up (3, 1.4%) and withdrawal of consent for personal reasons other than adverse events (1, 0.5%). Three of the 7 subjects who discontinued due to adverse events were in the PBO group, 2 were in the BRV 5 mg group and 1 each was in the BRV 20 and 50 mg groups.

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A general; overview of the treatment-emergent adverse events (TEAEs) recorded during the study, classified by UCB System Organ Class, is displayed below.

Safety Results	**PBO (N=54)**	**BRV 5 (N=50)**	**BRV 20 (N=52)**	**BRV 50 (N=52)**
Subjects with at least one TEAE n (%)	29 (53.7)	26 (52)	29 (55.8)	28 (53.8)
Subjects with at least one TEAE (by UCB System Organ Class)	**n (%) [n considered drug-related by Investigator]**			
Blood and lymphatic system disorders	1 (1.9)	4 (8.0)	4 (7.7)	2 (3.8)
Cardiac disorders	0	2 (4.0)	0	0
Ear and labyrinth disorders	0	0	1 (1.9)	0
Eye disorders	0	1 (2.0)	1 (1.9)	1 (1.9)
Gastrointestinal disorders	6 (11.1)	3 (6.0)	7 (13.5)	5 (9.6)
General disorders and administration site conditions	5 (9.3)[2]	0	3 (5.8)[2]	4 (7.7)[1]
Hepatobiliary disorders	2 (3.7)	1 (2.0)	1 (1.9)	2 (3.8)
Infections and infestations	9 (16.7)	7 (14.0)	6 (11.5)	8 (15.4)
Injury, poisoning and procedural complications	1 (1.9)	3 (6.0)	2 (3.8)	1 (1.9)
Metabolism and nutrition disorders	3 (5.6)[2]	1 (2.0)	4 (7.7)[3]	3 (5.8)[2]
Musculoskeletal and connective tissue disorders	2 (3.7)	2 (4.0)	3 (5.8)	2 (3.8)
Nervous system disorders	11 (20.4)[4]	8 (16.0)[4]	12 (23.1)[6]	8 (15.4)[6]
Pregnancy, puerperium and perinatal conditions	0	0	0	1 (1.9)[1]
Psychiatric disorders	2 (3.7)[2]	2 (4)[1]	3 (5.8)[1]	3 (5.8)[1]
Renal and urinary disorders	0	1 (2.0)	3 (5.8)	1 (1.9)
Respiratory, thoracic and mediastinal disorders	0	2 (4.0)	3 (5.8)	0
Skin and subcutaneous tissue disorders	2 (3.7)[1]	2 (4.0)[2]	1 (1.9)[1]	3 (5.8)[2]
Surgical and medical procedures	0	0	0	1 (1.9)
Vascular disorders	0	1 (2.0)	1 (1.9)	0

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Deaths, SAEs and Other significant AEs are displayed below.

Safety Results	**PBO (N=54)**	**BRV 5 (N=50)**	**BRV 20 (N=52)**	**BRV 50 (N=52)**
Deaths	0	0	0	0
Subjects with at least one SAE n(%)	0	0	1 (1.9)	0
Subjects with at least one SAE (by UCB System Organ Class)	**n(%) [n considered drug-related by the Investigator]**			
Nervous system disorders	0	0	1 (1.9)[1]	
Subjects with AEs leading to permanent study drug discontinuation(by UCB System Organ Class)	**n(%) [n considered drug-related by the Investigator]**			
Blood and Lymphatic System Disorders	1 (1.9)[1]	1 (2)	0	0
Nervous system disorders	1 (1.9)[1]	1 (2)[1]	1 (1.9)[1]	0
Psychiatric disorders	0	1 (2)[1]	0	0
Subjects with AEs leading to temporary study drug discontinuation (by UCB System Organ Class)	**n(%) [n considered drug-related by the Investigator]**			
Eye disorders	0	0	0	1 (1.9)[1]

Overall, the incidence of TEAEs reported in the 4 groups were similar: there were 29 (53.7%) subjects in the PBO group, 26 (52%) subjects in the BRV 5 mg group, 29 (55.8%) subjects in the BRV 20 mg group and 28 (53.8%) subjects in the BRV 50 mg group reporting at least one TEAE. The intensity of most of the TEAEs reported was mild to moderate. The most frequently reported TEAEs (preferred term) were in decreasing order: headache reported in 11 (5.2%) subjects, somnolence reported in 11 (5.2%) subjects, influenza reported in 9 (4.3%) subjects, dizziness reported in 8 (3.8%) subjects, neutropenia reported in 7 (3.4%) subjects and fatigue reported in 5 (2.4%) subjects.

Few drug-related TEAEs were reported and there were no medically relevant differences between the four groups. Six subjects, two in the PBO group, 3 in the BRV 5 mg group and 1 in the BRV 20 mg group permanently discontinued the study due to an AE. One treatment-emergent SAE was reported in the BRV 20 mg group and was considered drug-related by the Investigator. No death occurred during the study.

Analysis of changes from baseline in laboratory parameters did not reveal any trends. During the treatment period, no significant changes in vital sign parameters were observed. No significant weight changes were observed during the study.

Majority of the abnormal physical and neurological findings were not considered clinically significant by the Investigator. No trends emerged when comparing physical and neurological abnormalities between the treatment groups.

A majority of the subjects in each treatment group did not have any changes in their ECG during the study. No trends emerged when evaluating changes from baseline in ECG parameters.

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CONCLUSIONS:

The estimated percent reductions over placebo in partial onset seizure frequency per week for 5 mg/day, 20 mg/day and 50 mg/day are strongly suggestive of a dose response, with estimated values of 9.8%, 14.9% and 22.1% respectively. This clear dose trend is consistent with the results of all secondary efficacy analyses.

Brivaracetam was [redacted] and well tolerated in the dose range 5-50 mg/day with a similar incidence of adverse events in the placebo, 5 mg/day, 20 mg/day and 50 mg/day groups.

Report Date:
02-Nov-2006