N01114, 2004-001856-35

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

Sponsor:

UCB Pharma SA
Chemin du Foriest
B-1420 Braine-l´Alleud
Belgium

Official study title:

A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 used as adjunctive treatment at doses of 50 and 150 mg/day in b.i.d. administration (oral capsules of 25 mg) for a maximum of 12 weeks in subjects from 16 to 65 years with refractory epilepsy suffering from partial onset seizures whether or not secondarily generalized

2. SYNOPSIS

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product: *	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Title of Study:
A multicenter, double-blind, randomized, placebo-controlled, 3 parallel groups, dose-ranging trial evaluating the efficacy and safety of ucb 34714 used as adjunctive treatment at doses of 50 and 150 mg/day in b.i.d. administration (oral capsules of 25 mg) for a maximum of 12 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-two Investigators in nine countries actively participated (enrolled at least one subject) in this study.

Publication:
None at the time of this report.

Studied Period (years): **First Subject FirstVisit:** 11-May-2005 **Last Subject Last Visit:** 28-Mar-2006	**Phase of Development:** Phase II / Therapeutic exploratory

Objectives:
Primary objective: To evaluate the efficacy of brivaracetam at the doses of 50 and 150 mg/day in b.i.d. administration in reducing seizure frequency in subjects with focal epilepsy not fully controlled despite treatment with 1 or 2 concomitant antiepileptic drug(s) [AED(s)].
Secondary objectives: To evaluate the dose/clinical response relationship and narrow down the dose range of clinical interest, to explore tolerability of brivaracetam in the same population, and to collect data on seizure-free days and seizure-free subjects.
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. To explore the impact of brivaracetam on the overall evolution of seizure and epilepsy, health-related quality of life, anxiety and depression, and to collect data on the medical resources used.

Methodology:
This trial was designed as a double-blind, randomized, placebo-controlled, multicenter, 3 parallel groups, dose ranging study.

Number of Subjects:
It was foreseen to randomize 153 subjects (51 per group). Assuming a screen failure rate of 20%, 192 subjects were to be screened.

Diagnosis and Main Criteria for Inclusion:
Male/female subjects (16 - 65 years) suffering from refractory focal epilepsy, experiencing at least 4 partial onset seizures (whether or not secondarily generalized) per 4 weeks and taking one or two concomitant AED(s) at stable dose.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
brivaracetam (25 mg capsule)	50 or 150 mg/day in *b.i.d.* (oral administration)	[redacted]

*Approved as Briviact® (this note was added for clarification purposes afterwards)

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Duration of Treatment:
The study consisted of a 4-week Baseline period followed by a 10-week Treatment period (3-week Up-titration and 7-week Maintenance periods), followed by a 2-week Down-titration or Conversion Periods, and a 2-week Study-drug-free period (for subjects down-titrated). Subjects were exposed to brivaracetam during 12 weeks.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
Matching placebo capsule	Placebo (oral administration)	[redacted]

Criteria for Evaluation:
Efficacy:
Primary efficacy variable:

- Partial onset seizure frequency per week (type I) over the Maintenance period.

Secondary efficacy variables:

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

Exploratory variables:

- 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.
- Health-Related Quality of Life (QOLIE-31-P) assessed at the Randomization Visit and at the Evaluation Visit or Early Discontinuation Visit.
- Hospital Anxiety and Depression Scale (HADS) assessed at the Randomization Visit and at the Evaluation Visit or Early Discontinuation Visit.
- Medical resources used over the Baseline period and over the Treatment period, including health care provider consultations not foreseen by the protocol, concurrent medical procedures, concomitant medications, hospitalizations and length of stay.

Pharmacokinetic (PK) 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 (V1, V2), at each specified visit under trial drug and during the trial drug-free period (safety visit).

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Safety:

Safety was assessed by means of:

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

Statistical Methods:

The null hypotheses of no treatment difference during the Maintenance period between each randomized dose of brivaracetam versus placebo 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 brivaracetam 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 a linear mixed effects model for longitudinal data. The model included as factors randomization group – period interaction 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 during the Maintenance period between each randomized dose of brivaracetam and placebo were expressed as a percentage reduction over placebo, with 2-sided 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).

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

SUMMARY – CONCLUSIONS

EFFICACY RESULTS (primary and secondary efficacy variables):

Out of the 194 subjects screened, 157 (87 females, 70 males) aged between 16.5 and 65.6 years (mean [SD]: 37.5 [11.5]) were randomized into the study (52 in the placebo group [PBO], 53 in the brivaracetam 50 mg group [BRV 50], and 52 in the brivaracetam 150 mg group [BRV 150]); they constituted the ITT population. Out of these 157 subjects, 140 (49 PBO, 43 BRV 50, and 48 BRV 150) were included in the per-protocol (PP) analysis. One hundred forty-eight subjects (48 PBO, 51 BRV 50, and 49 BRV 150) completed the study. One hundred thirty-five subjects (41 PBO, 46 BRV 50, and 48 BRV 150) decided to enter a long-term follow-up study (study N01125).

Primary efficacy variable: (the primary efficacy analysis was carried out on both the ITT and PP populations)

The estimated percent reductions over placebo in the partial onset seizure frequency per week (type I) over the Maintenance period were 14.7% and 13.6% in respectively the BRV 50 and BRV 150 groups. Those reductions over placebo were not statistically significant at the 5% significance level (see table below).

Partial onset seizure frequency per week (type I) (Maintenance period)	**PBO N=52**	**BRV 50 N=53**	**BRV 150 N=52**
LS means (log transformed)	1.278	1.119	1.132
LS means (back-transformed)	2.590	2.062	2.103
Difference *vs.* Placebo			
% reduction over Placebo		14.7%	13.6%
2-sided 95% confidence interval		(-2.7%, 29.2%)	(-4.1%, 28.3%)
p-value		0.093	0.124

Linear mixed effects model with log transformed partial onset seizure frequency per week as response, period by treatment group interaction, log transformed baseline seizure frequency per week and stratification factors as independent variables

Percent reductions over placebo computed for the PP population were 15.2% and 10.6% in respectively the BRV 50 and BRV 150 groups. Those reductions over placebo were not statistically significant at the 5% significance level (2-sided).

Secondary efficacy variables: (the secondary efficacy analyses were carried out on the ITT population)

Since very few seizures of type II and type III were reported in the study, the results for all seizures (types I+II+III) are almost identical to the results for partial onset seizure (type I).

The median differences versus placebo for the percent reduction from Baseline in partial onset seizure frequency per week over the Maintenance period were 22.50% and 14.15% in respectively the BRV 50 and BRV 150 groups. The reduction over placebo in the BRV 50 group was statistically significant at the 2-sided 5% significance level (see table hereafter).

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Maintenance period	**PBO N=52**	**BRV 50 N=53**	**BRV 150 N=52**
Evaluable subjects	52	52	51
Median (Q1 – Q3)	18.92 (-22.08 – 43.21)	38.23 (9.38 – 65.15)	30.00 (1.48 – 61.90)
Median diff (*vs.* PBO)		-22.50%	-14.15%
95% 2-sided CI		(-40.00%, -3.04%)	(-34.03%, 4.13%)
p-value (Wilcoxon-Mann-Whitney test)		0.017	0.113

The odds ratios of being a 50% responder (*vs.* PBO) over the Maintenance period were 2.16 and 1.66 in respectively the BRV 50 and BRV 150 groups. Those ratios over placebo were not statistically significant at the 5% significance level (see table below).

Maintenance period	**PBO N=52**	**BRV 50 N=53**	**BRV 150 N=52**
Evaluable Subjects	52	53	51
Non-responder	40 (76.9%)	32 (60.4%)	34 (66.7%)
Responders	12 (23.1%)	21 (39.6%)	17 (33.3%)
Odds Ratio (BRV *vs.* PBO)		2.16	1.66
95% 2-sided CI		(0.92, 5.13)	(0.69, 3.99)
p-value		0.077	0.261

Logistic regression modeling probability of being a responder with treatment group, stratification factor and baseline seizure frequency as covariates.

The percentage reduction from Baseline in partial seizure frequency per week over the Maintenance period in the 5 pre-defined categories (< -25%, -25% to < 25%, 25% to < 75%, 75% to < 100%, and 100%) is given in the table hereafter. The proportions of subjects with at least 25% reduction from Baseline in partial seizure frequency per week were larger in the BRV groups compared to the PBO group. The overall difference in distribution was statistically significant in the BRV 50 group (p=0.048).

One (1.9%) subject in the PBO group, 5 (9.4%) in the BRV 50 group, and 3 (5.9%) in the BRV 150 group were seizure free (all seizures) during both the Maintenance and Treatment periods.

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Maintenance period	**PBO N=52**	**BRV 50 N=53**	**BRV 150 N=52**
Evaluable Subjects	52	53	52
< -25%	12 (23.1%)	7 (13.2%)	5 (9.8%)
-25% to < 25%	15 (28.8%)	12 (22.6%)	20 (39.2%)
25% to < 75%	21 (40.4%)	25 (47.2%)	18 (35.3%)
75% to <100%	3 (5.8%)	4 (7.5%)	5 (9.8%)
100%	1 (1.9%)	5 (9.4%)	3 (5.9%)
p-value (Cochran-Mantel-Haenszel test)		0.048	0.235

The median baseline seizure free days per 4 weeks was 22 days for both PBO and BRV 50 groups and 19 days in the BRV 150 group. The median seizure free days per 4 weeks during the Treatment period was 22, 24 and 22 days for respectively the PBO, BRV 50 and BRV 150 groups.

Times to the 1st, 5th, and 10th seizure (any seizure) during the Maintenance period were analyzed using a survival analysis model. No significant differences were found between BRV groups and placebo.

SAFETY RESULTS:
In this study, 52 subjects were exposed to PBO, 53 to BRV 50, and 52 to BRV 150 for about 12 weeks.

A general overview of the Treatment Emergent Adverse Events (TEAEs) recorded during the study, classified by UCB System Organ Class, is displayed herefater.

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Safety Results	**PBO (N=52)**	**BRV 50 (N=53)**	**BRV 150 (N=52)**
Subjects with at least one TEAE, n(%)	40 (76.9)	39 (73.6)	35 (67.3)
Subjects with at least one TEAE (by UCB System Organ Class)	**n(%) [n considered drug-related by the Investigator]**		
Blood and Lymphatic System Disorders	3 (5.8) [1]	2 (3.8) [1]	3 (5.8) [1]
Cardiac Disorders	1 (1.9) [0]	1 (1.9) [0]	1 (1.9) [1]
Ear and Labyrinth Disorders	3 (5.8) [2]	2 (3.8) [1]	1 (1.9) [0]
Eye Disorders	1 (1.9) [1]	0	3 (5.8) [2]
Gastrointestinal Disorders	13 (25.0) [9]	11 (20.8) [4]	9 (17.3) [6]
General Disorders and Administration Site Conditions	8 (15.4) [6]	8 (15.1) [7]	9 (17.3) [7]
Hepatobiliary Disorders	1 (1.9) [1]	2 (3.8) [2]	0
Infections and Infestations	11 (21.2) [0]	12 (22.6) [1]	10 (19.2) [0]
Injury, Poisoning and Procedural Complications	5 (9.6) [2]	3 (5.7) [1]	4 (7.7) [0]
Metabolism and Nutrition Disorders	3 (5.8) [1]	6 (11.3) [5]	4 (7.7) [4]
Musculoskeletal and Connective Tissue Disorders	10 (19.2) [4]	7 (13.2) [0]	1 (1.9) [0]
Nervous System Disorders	17 (32.7) [12]	16 (30.2) [12]	17 (32.7) [13]
Pregnancy, Puerperium and Perinatal Conditions	0	0	1 (1.9) [0]
Psychiatric Disorders	12 (23.1) [8]	8 (15.1) [6]	6 (11.5) [5]
Renal and Urinary Disorders	6 (11.5) [3]	1 (1.9) [0]	2 (3.8) [1]
Reproductive System and Breast Disorders	2 (3.8) [0]	1 (1.9) [0]	0
Respiratory, Thoracic and Mediastinal Disorders	3 (5.8) [0]	0	4 (7.7) [2]
Skin and Subcutaneous Tissue Disorders	4 (7.7) [2]	4 (7.5) [1]	1 (1.9) [1]
Vascular Disorders	1 (1.9) [1]	0	0

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

Death, SAEs, and Other Significant AEs			
Death, n (%)	0	0	0
Subjects with at least one SAE, n(%)	5 (9.6)	1 (1.9)	3 (5.8)
Subjects with at least one SAE (by UCB System Organ Class)	**n(%) [n considered drug-related by the Investigator]**		
Infections and Infestations	1 (1.9) [0]	1 (1.9) [0]	0
Injury, Poisoning and Procedural Complications	1 (1.9) [1]	0	1 (1.9) [0]
Musculoskeletal and Connective Tissue Disorders	1 (1.9) [0]	0	0
Nervous System Disorders	2 (3.8) [1]	0	1 (1.9) [0]
Pregnancy, Puerperium and Perinatal Conditions	0	0	1 (1.9) [0]
Subjects with AEs leading to permanent study drug discontinuation, n(%)	1 (1.9)	2 (3.8)	2 (3.8)
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	0	1 (1.9) [1]	1 (1.9) [0]
Nervous System Disorders	2 (3.8) [2]	0	1 (1.9) [1]
Pregnancy, Puerperium and Perinatal Conditions	0	0	1 (1.9) [0]
Psychiatric Disorders	0	1 (1.9) [1]	0
Subjects with AEs leading to temporary study drug discontinuation or dose changes, n(%)	1 (1.9)	2 (3.8)	4 (7.7)
Subjects with AEs leading to temporary study drug discontinuation or dose changes (by UCB System Organ Class)	**n(%)[n considered drug-related by the Investigator]**		
Ear and Labyrinth Disorders	1 (1.9) [1]	0	0
Gastrointestinal Disorders	1 (1.9) [1]	1 (1.9) [1]	0
Infections and Infestations	0	1 (1.9) [0]	0
Injury, Poisoning and Procedural Complications	0	0	1 (1.9) [0]
Nervous System Disorders	1 (1.9) [1]	1 (1.9) [1]	3 (5.8) [2]
Psychiatric Disorders	1 (1.9) [1]	1 (1.9) [1]	1 (1.9) [1]

Overall, the incidences of the TEAEs reported in the three treatment groups were similar: there were 40 subjects (76.9%) in the PBO group, 39 subjects (73.6%) in the BRV 50 group, and 35 (67.3%) in the BRV 150 group reporting at least one TEAE. The intensity of most of the TEAEs reported was mild to

Name of Sponsor/Company: UCB Pharma SA Belgium	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product:	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	

moderate.

The most frequently reported TEAEs (Preferred Term) were in decreasing order: headache (reported in 16 subjects [10.2%]), fatigue and nausea (14 subjects [8.9%]), nasopharyngitis (12 subjects [7.6%]), somnolence (11 subjects [7.0%]), and dizziness (10 subjects [6.4%]).

Few drug-related TEAEs were reported and there were no medically relevant differences between the three treatment groups.

Five subjects, one in the PBO group and two in each BRV group, permanently discontinued the study due to an AE.

Nine SAEs were reported by nine subjects, five in the PBO group, one in the BRV 50 group and three in the BRV 150 group. None of the SAEs reported in the BRV groups were considered as study drug related by the Investigator. No death occurred during the study.

The incidences of AEs frequently associated with the use of other AEDs (mainly somnolence and dizziness), were low and similar in the 3 treatment groups. No relevant psychiatric TEAEs were reported. No withdrawal seizures were observed after discontinuation of BRV.

No clinically relevant changes from baseline were observed in hematology and blood chemistry laboratory values. Incidences of individual abnormal laboratory values were low. No clinically relevant changes from baseline were observed in vital signs. No significant weight changes were observed during the study. No clinically relevant changes in the ECG measurements, including QTc duration values, were observed.

CONCLUSIONS:
The estimated percent reductions over placebo in the partial onset seizure frequency per week (type I) over the Maintenance period were 14.7% and 13.6% after respectively brivaracetam 50 mg/day and brivaracetam 150 mg/day. Those reductions over placebo were not statistically significant.

Despite the absence of statistically significant results on the primary endpoint, a clear differentiation from placebo was observed after brivaracetam 50 mg/day on some of the secondary efficacy analyses, with no evidence of additional benefit to the subject after brivaracetam 150 mg/day.

Brivaracetam was safe and well tolerated in the dose range 50 – 150 mg in *b.i.d.* administration.

Report Date:
31-May-2007