DEV/EDV/05216.2006

1. SYNOPSIS

Name of Sponsor/Company: UCB S.A. – Pharma Sector Belgium	Individual Study Table Referring to Module 5.3.4.2	*(For National Authority Use only)*
Name of Finished Product: Not applicable	Volume:	
Name of Active Ingredient: Brivaracetam (ucb 34714)	Page:	

Title of the study:
A randomized placebo-controlled, 2-way crossover, multicenter, single-blind study to explore the efficacy of ucb 34714 in a minimum of 40 subjects suffering from mild to moderate essential tremor after 14 days of multiple oral doses up to 400 mg *b.i.d.*, 50 mg or 200 mg capsules.

Investigator(s): 5 Investigators were involved:
Dr. [redacted] (principal Investigator)
Dr. [redacted]
Dr. [redacted]
Dr. [redacted]
Dr. [redacted]

Study Center(s): 5 centers in 4 European countries were involved:
Hopital César de Paepe, Brussels, Belgium
CHU de Lille, Lille, France
Neurology Clinic of Semmelweis University, Budapest, Hungary
Department of Neurology of Szpzoz Szpital, Wolomin, Poland
Neurological Department of Szpital Zachodni, Grodzisk Mazowiecki, Poland

Publication: There were no publications at the time of report generation.

Studied Period (years): 16-Feb-2004 to 01-Mar-2005	**Phase of Development:** Human Pharmacology, phase IIa.

Objectives:
The primary objective of this Phase IIa study was to explore by specific recorded neurological tests, the efficacy of brivaracetam (ucb 34714) monotherapy in patients suffering from mild to moderate essential tremor.
The secondary objective was to document the safety of brivaracetam (ucb 34714) in patients suffering from mild to moderate essential tremor.

Methodology:
Randomized, multicenter, single-blind, 2-way crossover, placebo-controlled, 14-day repeated administration study.

Number of Subjects:
48 patients were screened and 46 randomized.

Diagnosis and Main Criteria for Inclusion:
Male or female patients with mild to moderate essential tremor on stable study disease medication prior to screening.

Test Product:	**Dose and Mode of Administration:**	**Batch Numbers:**
Brivaracetam (ucb 34714)	50 mg capsules for oral administration → 200 mg capsules for oral administration →	12705 13830

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Duration of Treatment:
The clinical phase of the study lasted 7 weeks. A 7-day washout period preceded the 14-day single-blind placebo run-in period. This was followed by a crossover treatment period of 2 x 14 days. There was no washout between the 2 crossover periods.
The discharge visit was to take place at Day 50 (last study drug administration) or within 6 days after Day 50.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Numbers:**
Placebo	Matching 50 mg capsules → Matching 200 mg capsules →	12639 13398

Criteria for Evaluation:
Efficacy:
Efficacy variables:
Primary pharmacodynamic variable: percentage change from baseline of the summated tremor (STS) score after 2 weeks of treatment. Tremor score is based on the clinical rating scales on the following essential tremor tests (that are also video recorded and coupled to an electromyography (EMG) of the arms):

- Recordings while the subject is sitting in a resting position for 30 sec.
- Recordings with arms kept outstretched for 30 sec.
- Recordings of the finger-to-finger test for 30 sec (both sides).
- Recordings of the finger-to-nose test and for 30 sec (both sides).

Secondary pharmacodynamic parameters:

- the clinical rating scales of the individual items mentioned above, as well as the corresponding EMG and video recordings.
- Drawing of 3 spirals (using a validated scale).
- Copy the words « hopital national » or “egyetemi klinika” for the Hungarian site or “szpital powiatowy” for the Polish sites.
- Putting water from a bottle (250 mL) into a cup (both sides tested).
- Movements of upper limbs between 2 mechanical counters.
- 9 hole peg test, both hands.
- Subjective vigilance test by Bond & Lader Visual Analogue Scale (VAS).
- Activity of Daily Life questionnaire (ADL).

Apart from the spirography test and the counting of movements of upper limbs between 2 mechanical counters, the secondary pharmacodynamic variables were not cleaned or analyzed.

Safety:
Safety variables: adverse events, physical and neurological examination, vital signs, clinical laboratory tests and ECG.

Statistical Methods:
Analyses were performed on all patients whom enrolled prior to the decision of study termination that was taken on 08-Feb-2005.
The primary efficacy variables were analyzed by descriptive statistics. Treatment effect on summarized tremor scores and treatment comparison were further analyzed by means of ANOVAs; treatment, period and sequence were included in the ANOVA model. Since the study was prematurely terminated, the data on

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secondary pharmacodynamic variables were not formally cleaned or analyzed. However, results of two functional tests were checked for consistency: spirography and on the counting of movements of upper limbs between 2 mechanical counters for 30 seconds (carried out 3 times). An exploratory analysis by means of an ANOVA was performed on them (non previously planned for the abbreviated CSR).
Safety data were listed and tabulated. Adverse events are descriptively summarized by MedDRA V7.0 primary system organ class, preferred term and intensity; and by primary system organ class, preferred term and relationship to study drug. AEs leading to withdrawal are presented. Laboratory test results were described with absolute values, mean changes and shifts from baseline as well as individual abnormal results. Vital signs (blood pressure and heart rate), abnormalities in physical and neurological examinations and ECG observations are also described.

SUMMARY – CONCLUSIONS

EFFICACY / PHARMACOKINETIC / PHARMACODYNAMIC RESULTS:

Clinical assessment:
Treatment effect on STS and comparison from baseline (percentage change) as analyzed by means of ANOVAs showed the following:

- **Treatment Effect** on Summated Tremor Score (Percentage Change from Baseline)

Treatment	LSMean	Standard Error	p-value
Placebo	-5.76	5.33	0.29
BRV 200 mg *b.i.d.*	-4.86	5.84	0.41
BRV 400 mg *b.i.d.*	-16.8	7.41	**0.02**

NB: 39 subjects were on BRV 200 mg: 20 subjects were in the placebo → BRV sequence and 19 in the BRV → placebo sequence.
7 subjects were on BRV 400 mg: 4 subjects were in the placebo → BRV sequence and 3 in the BRV → placebo sequence.

Overall, BRV 400 mg *b.i.d.* had a significant effect on decreasing the Summated Tremor Score, and BRV 200 mg *b.i.d.* had no significant effect, almost the same as placebo.

- **Treatment Comparison** of Summated Tremor Score (Percentage Change from Baseline)

Comparison	LSMean	Standard Error	p-value	90% CI
BRV 200 mg *b.i.d.* ↔ PLC	0.892	3.42	0.79	(-4.75; 6.54)
BRV 400 mg *b.i.d.* ↔ PLC	-11.0	7.46	0.14	(-23.3; 1.27)

NB: 39 subjects were on BRV 200 mg: 20 subjects were in the placebo → BRV sequence and 19 in the BRV → placebo sequence.
7 subjects were on BRV 400 mg: 4 subjects were in the placebo → BRV sequence and 3 in the BRV → placebo sequence.

No significant difference between placebo and BRV was shown for any of the BRV dosages (all 90% CI include 0).

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Functional testing: Spirography and mechanical counting of movements of upper limbs.
Overall, the 2 analyzed functional tests for essential tremor showed no statistical difference between 400 mg *b.i.d.* and placebo. There was also no statistical difference for the spirography test between 200 mg *b.i.d.* and placebo. For the mechanical counter test, 200 mg *b.i.d* was significantly worse than PLC.

SAFETY RESULTS:

- Irrespective of the causality assessment, somnolence and dizziness were the most frequently TEAEs in patients receiving BRV with higher occurrences than in patients under PLC: 36% versus 16% for somnolence and 18% versus 2% for dizziness.
- A BRV dose relationship is suggested as far as the incidence of the above AEs is concerned, however due to the small number of patients on the highest tested BRV dose of 400 mg *b.i.d.*, one should be cautious in interpreting these observations. The intensity of somnolence and dizziness does not appear to be dose-related.
- Vertigo, abnormal gait and hypotension were more frequently reported under BRV as compared to PLC: 11% versus 5%, 9% versus 2% and 8% versus 2% respectively.
- No serious adverse events were reported.
- None of the adverse events reported under BRV led to permanent study drug discontinuation.
- Hematology, blood biochemistry and urinalysis did not reveal any particular concern.
- The monitoring of vital signs (blood pressure and pulse rate) did not reveal any point of concern.
- ECG findings did not reveal any point of concern related to the BRV administration.

CONCLUSIONS:

Based on the mean of percentage change from baseline in summated tremor scores related to the upper limbs (clinical rating scales of 4 essential tremor tests), and within the limits of the present study, there is no apparent benefit of BRV 200 mg *b.i.d.* or BRV 400 mg *b.i.d.* as compared to PLC, on clinical signs of essential tremor, in patients suffering from mild to moderate essential tremor. Results of functional evaluation of essential tremor by means of spirography and counting of upper limbs movements within a specific timeframe did not show an apparent benefit of BRV 200 mg *b.i.d.* or BRV 400 mg *b.i.d.* as compared to PLC.

The safety profile observed in the present study N01129 is in line with the findings presented in the Investigator's Brochure dd 19-Sep-05.

Report Date: 25-Sep-2006