



N01162, 2004-000975-32

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB S.A. - Pharma Sector
Chemin du Foriest
B-1420 Braine-l'Alleud
BELGIUM

Official study title:

An exploratory, double blind, randomized, placebo-controlled, parallel group, multicenter study, for the assessment of efficacy, safety and tolerability of ucb 34714 50 mg oral capsules in b.i.d. administration at the doses of 200 mg/day and 400 mg/day, in subjects (at least 18 years old) suffering from post-herpetic neuralgia (PHN)



DEV/EDV/05020.2006

1. SYNOPSIS

Name of Sponsor/Company: UCB S.A. Belgium	Individual Study Table Referring to Module 5.3.5	(For National Authority Use only)
Name of Finished Product: NA *	Volume:	
Name of Active Ingredient: Brivaracetam	Page:	
Title of Study: An exploratory, double blind, randomized, placebo-controlled, parallel group, multicenter study, for the assessment of efficacy, safety and tolerability of ucb 34714 50 mg oral capsules in <i>b.i.d.</i> administration at the doses of 200 mg/day and 400 mg/day, in subjects (at least 18 years old) suffering from post-herpetic neuralgia (PHN).		
Investigator(s): [REDACTED], MD ([REDACTED]), study coordinator.		
Study Center(s): A total of 52 centers from the following countries: [REDACTED]		
Publication: Not applicable.		
Studied Period (years): 11-Oct-2004 to 05-Jan-2006	Phase of Development: Phase II / Therapeutic exploratory	
Objectives: Primary objective <ul style="list-style-type: none">To evaluate the efficacy of brivaracetam administered at two different doses (200 mg/day and 400 mg/day), using a placebo as control, in the treatment of PHN. Secondary objective <ul style="list-style-type: none">To explore the safety and tolerability of brivaracetam in the same indication. Exploratory objectives <ul style="list-style-type: none">To explore the impact on subject's self-reported health status.To collect data on pain free days and on medical resources used during the study.		
Methodology: Double-blind, multicenter, randomized, placebo controlled, parallel group study.		
Number of Subjects (planned): Two-hundred (200) screened, 150 randomized, 50 per treatment group.		
Diagnosis and Main Criteria for Inclusion: <ul style="list-style-type: none">Male/female subjects aged 18 years and older with ≥ 6 months pain after the healing of a herpes zoster skin rash.Pain intensity score assessed on an 11-point numerical pain rating scale with a score ≥ 4 at the screening visit and mean pain severity score ≥ 4 during the baseline period as evaluated on a minimum of 4 days.		
Test Product: Brivaracetam (50 mg capsule)	Dose and Mode of Administration: 100 mg <i>b.i.d.</i> or 200 mg <i>b.i.d.</i> administered orally	Batch Number: [REDACTED]
Duration of study (by subject): The maximum study duration per subject was seven weeks: one week placebo (baseline period), four weeks brivaracetam (BRV) 200 mg/day, or BRV 400 mg/day, or placebo (treatment period), two weeks drug free (drug-free period).		

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



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Reference Therapy: Placebo capsules	Dose and Mode of Administration: Oral administration		Batch Number: [REDACTED]
Criteria for Evaluation:			
Efficacy:			
The primary efficacy variable is:			
<ul style="list-style-type: none">The percent change in the average pain intensity score on an 11-point numerical pain rating scale from the baseline period to the last week of the treatment period.			
The secondary efficacy variables are:			
<ul style="list-style-type: none">The responder rate in average pain intensity score (11-point numerical pain rating scale). A responder is defined as a subject with a $\geq 30\%$ reduction in average pain intensity score at the last week of the treatment period compared to the baseline period.Percent change from the baseline period to each weekly mean in the pain intensity score.Percent change from the baseline period to each weekly mean, and to the last week of the treatment period, in the sleep interference score (11-point numerical sleep interference rating scale).Absolute change from the randomization visit to the evaluation/early discontinuation visit, in each score (Total pain score, Sensory score, Affective score, Present Pain Intensity (PPI) and Visual analogue Scale (VAS)) of the Short-Form McGill Pain Questionnaire (SF-MPQ).Patient's Global Evaluation Scale at the evaluation/early discontinuation visit.Investigator's Global Evaluation Scale at the evaluation/early discontinuation visit.Percent change from randomization visit to the evaluation/early discontinuation visit in the brush evoked allodynia intensity assessed by the subject on an 11-point numerical rating scale.Percent change from randomization visit to the evaluation/early discontinuation visit in the brush-evoked allodynia area (body, face) measured by the Investigator.			
The exploratory efficacy variables are:			
<ul style="list-style-type: none">EQ-5D dimensions at randomization visit and at evaluation/early discontinuation visit.Change from randomization visit to the evaluation/early discontinuation visit in the EQ-5D VAS.Pain free days over the baseline period and over the treatment period.Medical resources used over the baseline and treatment periods, including health care provider consultations not foreseen by the protocol and concomitant medications.			
Safety:			
Safety was assessed through:			
<ul style="list-style-type: none">Adverse Events and Serious Adverse Events reporting.Laboratory tests, including brivaracetam plasma levels.Electrocardiogram (ECG) measurements.Physical and neurological examinations.Vital signs.Body weight.			

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Statistical Methods:

The treatment groups were compared with respect to the primary efficacy variable using, as primary analysis, an Analysis of Covariance (ANCOVA) model. This model includes baseline average pain intensity score as covariate and treatment as factor. Comparison of each dose of brivaracetam versus placebo was performed. Difference in treatment LSMEANS between each dose of brivaracetam and placebo were computed with a 95% 2-sided confidence interval.

For the primary efficacy variable, the interaction between treatment group and the baseline average pain intensity score as well as the consistency of treatment group effect across pooled sites was explored.

Statistical methods used for secondary efficacy variables were: logistic regression (responder rate), and ANCOVA (sleep interference score at last week of the treatment period and SF-MPQ at evaluation visit).

Continuous variables at each week of the Treatment Period (pain intensity score, sleep interference score), allodynia related variables, and Patient and Investigator's Global Evaluation Scale were analyzed descriptively by treatment group.

Descriptive analysis by treatment group was done on exploratory efficacy variables.

Safety parameters were listed and analyzed descriptively by treatment group.

Statistical analyses were carried out according to a separate Statistical Analysis Plan (SAP).

SUMMARY – CONCLUSIONS

The ITT population included 152 subjects (51 subjects randomized to placebo, 50 randomized to BRV 200 mg/day and 51 randomized to BRV 400 mg/day). Ninety percent of subjects completed the study in placebo, 94.1% in BRV 200 mg/day and 88.2% in BRV 400 mg/day.

Age distribution was similar in the three treatment groups with a mean of 66 years. Overall, female subjects accounted for 57% of the population versus 43% male subjects. Median duration of herpes zoster skin rash was 22 days in placebo versus 31 days in both BRV treatment groups. Median duration of PHN was 19.7 months in placebo versus 14.4 months in BRV 200 mg/day and 23.8 months in BRV 400 mg/day.

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EFFICACY RESULTS:

The primary endpoint of this study was to evaluate the efficacy of BRV administered at two different doses (200 mg/day and 400 mg/day), using a placebo as control, in the treatment of PHN. The primary efficacy variable was the percent change in the average pain intensity score from the baseline period to the evaluation week (last week of the treatment period). Summary statistics of the primary efficacy variable revealed similar results in all three treatment groups (median change from baseline of 23.39% for placebo, 20.00% for BRV 200 mg/day and 22.95% for the BRV 400 mg/day). An analysis of covariance performed with the baseline average pain intensity score as the covariate showed no difference in pairwise comparisons between the treatment groups (p-values > 0.8).

Similar analyses to that of the primary efficacy variable were performed on the PP population, similar statistics were obtained in the 3 treatment groups and in the analysis of covariance, where none of the 3 pairwise comparisons revealed a statistical significant difference between treatment groups (p-values > 0.8).

A logistic regression carried out on responder rate (i.e. a subject with a $\geq 30\%$ reduction in average pain intensity score at the evaluation week (last week of the treatment period) compared to the baseline period), revealed no difference in pairwise comparison between the treatment groups (p-values > 0.4).

The means and medians of the percent reduction from the baseline period (of each weekly average) in pain intensity score, increased from week 1 to week 4 in a similar way in the three treatment groups. In a similar fashion to the pain intensity score, the sleep interference score, revealed no treatment effect in favor of brivaracetam in the means and medians of the weekly percent change from baseline. Taking the baseline average sleep interference score as the covariate, an analysis of covariance was performed on the percent change from the baseline period to the evaluation week (last week of the treatment period). Pairwise comparisons between treatment groups showed no statistical significant differences at 5%.

The absolute change between randomization visit and evaluation/early discontinuation visit was investigated in the following variables of the SF-MPQ questionnaire: total pain score; sensory score; affective score; present pain intensity and visual analogue scale (VAS). For these variables similar results were observed in the 3 treatment groups. An analysis of covariance for each variable, showed no statistical difference in pairwise comparisons between the treatment groups.

In the subset of subjects with allodynia at baseline, the percent change between randomization visit and evaluation/early discontinuation visit was investigated in brush-evoked allodynia area as assessed by the Investigator and allodynia pain intensity as assessed by the subject. In the case of allodynia pain intensity, no difference in favor of brivaracetam was observed between the treatment groups. In the case of allodynia body area, the means and medians between the randomization visit and evaluation /early discontinuation visit were greater in BRV 400 mg/day than the other two groups. The variability was also greater in this treatment group.

The subject's and the Investigator's global evaluation at the evaluation/early discontinuation visit showed a similar number of subjects improved in the 3 treatment groups, reinforcing the idea that there is no treatment effect in favor of brivaracetam.

Exploratory efficacy variables did not reflect a treatment effect either for the following reasons: slight to moderate improvements were observed in each of the 5 EQ-5D dimensions and the VAS, independently of the treatment group; a large majority of patients reported zero pain-free days during the treatment period, results were not interpreted further; there were slightly more unplanned consultations and non-PHN medications started in the treatment period in the placebo group versus the BRV 400mg group per day, whereas the use of PHN medication was comparable in all groups.



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<p>SAFETY RESULTS:</p> <p>No deaths occurred during the study but 1 subject (██████████) reported three consecutive SAEs (2 vascular purpuras and 1 thrombocytopenia) on BRV 400 mg/day with possible relationship to study drug.</p> <p>The most frequent TEAEs (treatment-emergent adverse events, that includes post-treatment events) were reported by primary SOC in the “Nervous System Disorders” (7 subjects, 14% in placebo and 28 subjects, 27% in BRV), “General Disorders and Administration Site Conditions” (5 subjects, 10% in placebo and 18 subjects, 17.6% BRV), “Gastrointestinal Disorders” (5 subjects, 10% placebo and 10 subjects 9.8% BRV), and “Ear and Labyrinth Disorders” (1 subject, 2.0% placebo and 10 subjects, 9.8% BRV).</p> <p>The most frequently reported TEAEs (incidence \geq 5% in one of the treatment group and treatment difference versus placebo of at least 5%) were, by preferred term: fatigue (5.9% 200 mg/day BRV, 11.8% 400 mg/day BRV and 4.0% placebo); headache (7.8% 200 mg/day BRV, 3.9% 400 mg/day BRV and 2.0% placebo); nausea (2.0% 200 mg/day BRV, 7.8% 400 mg/day BRV and 2.0% placebo), somnolence (15.7% 200 mg/day BRV, 15.7% 400 mg/day BRV and 4.0% placebo) and vertigo (13.7% 200 mg/day, 5.9% 400 mg/day and 2.0% placebo).</p> <p>The number (%) of subjects with TEAEs that led to dose change were: one (2.0%) in the placebo group, three (5.9%) in 200 mg/day group and 5 (9.8%) in BRV 400 mg/day group.</p> <p>The number (%) of subjects with TEAEs that led to temporary study drug discontinuation were: one (2%) in the placebo group and one (2%) in the BRV 400 mg/day group.</p> <p>The number (%) of subjects with TEAEs that led to permanent study drug discontinuation were: three (6%) in Placebo group; one (2%) in BRV 200 mg/day group and four (7.8%) in BRV 400 mg/day group.</p> <p>Amongst the TEAEs reported, sixteen were post-treatment AEs (5 in PBO group, 2 in BRV 200 mg/day group, and 9 in BRV 400 mg/day group. They were reported in 10 subjects (3 subjects (6.0%) in PBO group, 2 subjects (3.9%) in BRV 200 mg/day group, and 5 subjects (9.8%) in BRV 400 mg/day group.</p> <p>Overall, across visits and between the three treatment groups no important changes or trends were observed in hematology and biochemistry parameters.</p> <p>Vital signs, physical and neurological examinations, weight and ECG revealed no major trends across the treatment groups.</p> <p>CONCLUSIONS:</p> <p>Based on this 4 -week treatment study:</p> <p>BRV at doses of 200 mg/day and 400 mg/day was not superior to placebo in the treatment of PHN.</p> <ul style="list-style-type: none"> BRV displayed a good safety and tolerability profile in subjects suffering from PHN in terms of adverse events profile and drop-out rate. 		
<p>Final Synopsis: 20-Oct-2006</p>		

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