



2. SYNOPSIS

Name of Sponsor/Company: UCB Pharma SA	Individual Study Table Referring to Module	<i>(For National Authority Use only)</i>
Name of Finished Product: Brivaracetam	Volume:	
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Title of Study: A multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of brivaracetam used as adjunctive treatment for 12 weeks in adolescent and adult patients (≥ 16 years) with genetically ascertained Unverricht-Lundborg disease		
Investigator(s): Eighteen Investigators in 8 countries actively participated in the study.		
Study Center(s): Eighteen sites in 8 countries participated in the study and enrolled 1 or more subjects.		
Publication: None as of the time of this report.		
Studied Period (years): First subject enrolled: 07 Nov 2006 Last subject completed: 08 Jan 2008		Phase of Development: Therapeutic confirmatory/Phase 3
Objectives: Primary Objective The primary objective of the study was to compare the efficacy of brivaracetam (BRV) 5mg/day and 150mg/day in bid administration with placebo, on the symptom relief of Action Myoclonus in patients with ULD. Secondary Objectives The secondary objectives were to compare the efficacy of BRV 5mg/day and 150mg/day in bid administration with placebo on the functional disability, stimulus sensitivity and on the symptom relief as evaluated by the Myoclonus Patient Questionnaire in patients with ULD. The secondary objectives were also to evaluate the dose/clinical response relationship, to assess the safety and tolerability of BRV in this patient population as well as to assess the effect of BRV on the global evaluation of the disease evolution (assessed by the Investigator) in patients with ULD.		



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Exploratory objectives The exploratory objectives were to evaluate the effect of BRV on patient functioning as assessed by the QOLIE-31-P and HADS and on the global evaluation of the evolution of the disease (assessed by the patients) in patients with ULD.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel study to evaluate the efficacy and safety of BRV at doses of 5mg/day and 150mg/day in bid administration (oral tablets of 2.5mg, 25mg, 50mg, and matching PBO) as adjunctive treatment in adolescent and adult subjects (≥ 16 years) with genetically ascertained ULD. Subjects were centrally randomized to PBO, BRV 5mg or BRV 150mg in a ratio of 1:1:1. The randomization was stratified for concomitant use of piracetam (PIR) or levetiracetam (LEV). Brivaracetam or PBO were administered for 16 weeks, consisting of an Up-titration Period, Maintenance Period followed by either a Conversion Period (for subjects entering the Long-term Follow-up [LTFU] study) or by a Down-titration Period and a 2-week Drug-free period (for subjects not entering the LTFU study).		
Number of Subjects: To have 39 completed subjects, it was planned to have 45 subjects randomized. A total of 72 subjects were screened, and 56 subjects were randomized.		
Diagnosis and Main Criteria for Inclusion: <ul style="list-style-type: none">• Subjects with diagnosed ULD ascertained by appropriate genetic testing for a homozygous or compound heterozygous mutation in the cystatin B (CSTB) gene.• Subjects with moderate to severe myoclonus documented by an Action Myoclonus sum score of ≥ 30 (evaluation by Investigator).• Subjects treated or having been treated with clonazepam up to the maximum recommended daily dose of 20mg or up to their individual optimal dose, or maximum tolerated dose (MTD), as assessed by the Investigator. The reason for discontinuation or for maintenance at a dose lower than the maximum recommended daily dose had to be specified in the case report form (CRF) (eg, adverse effect or significant risk thereof, lack or loss of efficacy).• Subjects treated or having been treated with valproic acid up to the maximum recommended daily dose 60mg/kg or serum levels of 100μg/ml or up to their individual optimal dose, or MTD, as specified by the Investigator. The reason for discontinuation or for maintenance at a dose lower than the maximum recommended		

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<p>daily dose had to be specified in the CRF (eg, adverse effect or significant risk thereof, lack or loss of efficacy).</p> <ul style="list-style-type: none"> • Concomitant antiepileptic drugs(s) (AED[s]) stable from at least 1 month before Visit 1 and during the whole study period. • Male/female subjects from 16 years onwards. Subjects under 18 years could only be included where legally permitted and ethically accepted. 		
Test Product: Brivaracetam	Dose and Mode of Administration: Oral tablet of 2.5mg Oral tablet of 25mg Oral tablet of 50mg	Batch Number: 14921, 14963, 15343, 14910, 15136, 15137, 14911
Duration of Treatment: Treatment consisted of a 2-week Up-titration Period, a 12-week Maintenance Period and a 2-week Conversion Period or Down-titration Period (for subjects not entering a LTFU study).		
Reference Therapy: Placebo	Dose and Mode of Administration: Matching 2.5mg PBO tablet Matching 25mg PBO tablet Matching 50mg PBO tablet	Batch Number: 15127, 14909, 14912, 14927
Criteria for Evaluation:		
<p>Efficacy: The primary efficacy variable was the percent reduction from Baseline on the centrally read Action Myoclonus score (UMRS Section 4) as assessed at the end of the treatment or at study end.</p> <p>The secondary efficacy variables were:</p> <ul style="list-style-type: none"> • The percent reduction from Baseline on the Functional Disability as per UMRs Section 5. • The percent reduction from Baseline on the Stimulus Sensitivity (UMRS Section 3). • The percent reduction from Baseline on the Myoclonus Patient Questionnaire (UMRS Section 1). • Global Evaluation Scale (I-GES). 		

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<p>The exploratory variables were:</p> <ul style="list-style-type: none">• The QOLIE-31-P subscales scores (seizure worry, overall quality of life, emotional well-being, energy/fatigue, cognitive functioning, medication effects and social function), the Total Score and the Health Status Item Score.• The HADS scale scores (Anxiety and Depression).• The Patient's Global Evaluation Scale (P-GES).		
<p>Safety: Safety variables included treatment-emergent adverse events (AEs), physical examination assessments, clinical laboratory results (hematology, blood chemistry and urinalysis), ECGs, vital signs (including body weight), plasma BRV levels, and plasma AED/AMD levels.</p> <p>The seizure frequency was assessed for generalized tonic-clonic seizures and for all seizures altogether.</p>		
<p>Statistical Methods: For the evaluation of efficacy, summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum and maximum [with 25th and 75th percentiles as optional]) were tabulated. All statistical tests were carried out 2-tailed at the 5% level of significance unless otherwise stated. Statistical hypothesis testing was not performed for demographic, other selection characteristics, or safety variables. Unless otherwise specified, all analyses were presented by treatment group.</p> <p>The efficacy analyses were performed on the ITT population. In order to control for multiplicity, the first hypothesis for the primary efficacy variable that was tested compared placebo versus the pooled BRV doses. If this hypothesis was rejected (at 5%), both pairwise comparisons of placebo versus each BRV dose were tested at 5%.</p> <p>The primary analysis was a nonparametric endpoint analysis at Last Treatment Visit (Last Observation Carried Forward) based on the Wilcoxon test, stratified for concomitant use of PIR or LEV. The treatment effect was estimated by the unstratified Hodges-Lehmann estimate of the difference between the pooled BRV doses, or individual doses, and placebo.</p> <p>In case the number of subjects with major protocol deviations affecting the primary efficacy endpoint exceeded 10%, the primary efficacy analysis was also conducted on the</p>		



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per-protocol (PP) population.

Several sensitivity analyses were planned to investigate the consistency of the treatment effect:

A longitudinal model was fit to the centrally read Action Myoclonus score percent reduction from Baseline scores over the treatment period with treatment by visit interaction, stratification factor (concomitant use of PIR or LEV) and Baseline as explanatory variables and no constraints on the covariance structure.

A nonparametric analysis similar to the primary analysis was performed on the centrally read Action Myoclonus score absolute reduction from Baseline at the Last Treatment Visit.

A sensitivity analysis of the centrally read Action Myoclonus score percent reduction from Baseline at the Last Treatment Visit consisted of an ANCOVA model with stratification factor (concomitant use of PIR or LEV) and Baseline as explanatory variables.

The centrally read Action Myoclonus score percent reduction from Baseline averaged over the treatment period was analyzed using an ANCOVA model with stratification factor (concomitant use of PIR or LEV) and Baseline as explanatory variables.

Estimates of the centrally read Action Myoclonus score percent reduction from Baseline over the treatment period within strata as well as combination of strata were obtained using the previously defined longitudinal model with stratum by treatment interaction. In case the primary endpoint showed a statistically significant result for each of the doses, the secondary endpoints were to be tested for placebo versus the pooled BRV doses. The testing scheme would be hierarchical, meaning that reaching statistical significance (at 5%) on a secondary endpoint is a necessary condition to continue testing at 5% significance level for the next secondary endpoint. The secondary endpoints would be tested in the following order:

- Functional disability (UMRS Section 5)
- Stimulus sensitivity (UMRS Section 3)
- Myoclonus patient questionnaire (UMRS Section 1)

The analysis of the secondary variables was a nonparametric analysis.

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The Global Evaluation Scale by Investigator (I-GES) was compared between placebo and each dose at 5% significance level independently from the previous secondary endpoints, using the Wilcoxon test, stratified for concomitant use of PIR or LEV.		
SUMMARY – CONCLUSIONS: EFFICACY RESULTS: Demographic characteristics, types and precipitation factors of myoclonus, and prior and concomitant medication use were similar between the 3 groups. A majority of the subjects were taking LEV (30.4%), PIR (19.6%) or both (16.1%) at randomization. The study failed to demonstrate a treatment effect of BRV versus PBO for the primary efficacy endpoint, the percent reduction from Baseline in the centrally read Action Myoclonus score at the Last treatment Visit. The median percent reduction from Baseline in the centrally read Action Myoclonus score at the last treatment visit was 17.45% for the PBO group, 12.34% for the BRV 150mg/day group, and -4.6% for the BRV 5mg/day group. Further testing of the secondary endpoints could only be performed for indicative purposes. Results for Functional Disability Score and Stimulus Sensitivity Score, did not show any clear differences between the 3 treatment groups. The secondary endpoint of Myoclonus Patient Questionnaire showed a tendency toward beneficial effect of BRV 150mg/day compared to BRV 5mg/day and PBO. The secondary endpoint of I-GES showed a slight beneficial effect of BRV 150mg/day compared to BRV 5mg/day and PBO. Several pre-planned exploratory efficacy analyses were performed. The QOLIE-31-P, HADS, and P-GES showed no clear differences between the treatment groups however, there was a favorable trend in the overall quality of life score and seizure worry QOLIE-31-P scores for the BRV 150 mg/day group.		
SAFETY RESULTS: The ITT population consisted of 18 subjects in the PBO group, 20 subjects in the BRV 5mg/day group and 18 subjects in the BRV 150mg/day group. Treatment consisted of a 2-week Up-titration Period, a 12-week Maintenance Period, and a 2-week Conversion Period or Down-titration Period (for subjects not entering a LTFU study).		

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The proportion of subjects experiencing at least 1 AE during the entire study was 72.2% in the PBO group compared to 80.0% in the BRV 5mg/day group and 83.3% in the BRV 150mg/day group. Amongst these subjects, 2 subjects (1 [5.6%] each in the PBO and BRV 150mg/day groups) had AEs leading to permanent discontinuation of study drug, and 1 (5.0%) subject in the BRV 5mg/day group had an AE leading to temporary discontinuation of study drug. The proportion of subjects with drug-related AEs was 50.0% in the PBO group, 55.0% in the BRV 5mg/day group, and 61.1% in the BRV 150mg/day group. Two subjects (11.1%) in the PBO group, 3 subjects (15.0%) in the BRV 5mg/day group, and 2 subjects (11.1%) in the BRV 150mg/day group experienced an SAE. There were no deaths during the study.

A higher percentage of subjects in the BRV 150mg/day group (82.4%) experienced at least 1 AE during the Maintenance Period compared to the PBO (55.6%) and BRV 5mg/day (55.0) groups. As subjects progressed from the Up-titration Period to the Maintenance Period, the percentage of subjects with AEs remained similar for the PBO (55.6% in both periods) and BRV 5mg/day (slight increase from 45.0% in the Up-titration Period to 55.0% in the Maintenance Period) groups, however the percentage of subjects with AEs in the BRV 150mg/day group increased from 38.9% during the Up-titration period to 82.4% in the Maintenance period. During the Conversion Period, a slightly higher percentage of subjects in the BRV 5mg/day group (53.3%) reported AEs compared to the PBO group (35.7%) and the BRV 150mg/day group (14.3%).

For all 3 treatment groups, the greatest number of subjects reported an AE in the classification "Nervous system disorder." The second greatest number of subjects reported an AE in the classification "Infections and infestations" (PBO and BRV 5mg/day group) and "Gastrointestinal disorders" (BRV 150mg/day group).

"Headache", "myoclonus", and "somnolence" were the most commonly reported AEs. "Headache" was reported for 7 subjects (38.9%) in the PBO group, 3 subjects (15.0%) in the BRV 5mg/day group and 2 subjects (11.1%) in the BRV 150mg/day group. "Somnolence" was reported for 2 subjects (11.1%) in the PBO group, 3 subjects (15.0%) in the BRV 5mg/day group, and 4 subjects (22.2%) in the BRV 150mg/day group. "Myoclonus" was reported for 1 subject (5.6%) in the PBO group, 4 subjects (20.0%) in the BRV 5mg/day group, and 3 subjects (16.7%) in the BRV 150mg/day group.

The majority of AEs that were reported by more than 1 subject were considered drug-related by the Investigator (possible, probable, and highly probable relationship).



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<p>“Headache” was the most frequently reported drug-related AE (5 subjects in the PBO group, 2 subjects in the BRV 5mg/day group, and no subjects in the BRV 150mg/day group), followed by “somnolence” (2 subjects in the PBO group, 3 subjects in the BRV 5mg/day group, and 4 subjects in the BRV 150mg/day group).</p> <p>Mildly intense AEs were reported by 3 subjects (16.7%) in the PBO group, 4 subjects (20.0%) in the BRV 5mg/day group, and 5 subjects (27.8%) in the BRV 150mg/day group. Moderately intense AEs were reported by 8 subjects (44.4%) in the PBO group, 9 subjects (45.0%) in the BRV 5mg/day group and 6 subjects (33.3%) in the BRV 150mg/day group. Severely intense AEs were reported by 2 subjects (11.1%) in the PBO group, 3 subjects (15.0%) in the BRV 5mg/day group and 4 subjects (22.2%) in the BRV 150mg/day group.</p> <p>The 10 reported SAEs were in the classification “Nervous system disorder” (5 events; 2 in one subject), “Psychiatric disorders”, “General disorders and administration site conditions”, “Infections and infestations” (2 subjects), “Injury poisoning and procedural complications”. Seven subjects reported 10 SAEs during the study; 2 subjects in the PBO group (1 subject had 3 SAEs), 3 subjects in the BRV 5mg/day group, and 2 subjects in the BRV 150mg/day group (1 subject had 2 SAEs). One subject in the PBO group permanently discontinued due to convulsions, which were considered highly probably related to study drug.</p> <p>Two subjects permanently discontinued study drug due to an AE. One subject in the PBO group permanently discontinued due to the SAE “convulsion”, which was considered highly probably related to study drug and resolved after 39 days. One subject in the BRV 150mg/day group permanently discontinued due to “coordination abnormal” and “myoclonus”; both were considered possibly related to study drug and ongoing at study end.</p> <p>Fourteen subjects reported at least 1 psychiatric AE (7 in the PBO group, 6 in the BRV 5mg/day group, and 1 in the BRV 150mg/day group). One psychiatric event (“attention-seeking behaviour” for subject ██████████ in the PBO group) was reported as serious. The relationship of the psychiatric AEs to study drug varied from unlikely to probable.</p> <p>Few PCS hematology or blood chemistry values were presented by more than 1 subject in any treatment group during the Treatment or Conversion Periods of the study. Most of the</p>		

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<p>PCS blood chemistry values were presented in the PBO and BRV 5mg/day groups. Three subjects in the PBO group, 4 subjects in the BRV 5mg/day group, and 2 subjects in the BRV 150mg/day group presented PCS hematology values. Three subjects in the PBO group, 7 subjects in the BRV 5mg/day group, and 2 subjects in the BRV 150mg/day group presented PCS blood chemistry values.</p> <p>No clinically relevant changes from Baseline were observed for any vital sign parameters.</p> <p>There were no trends for increases in seizure frequency per week during treatment with BRV or PBO compared to Baseline.</p> <p>None of the ECG abnormalities that were observed were clinically significant.</p> <p>The results demonstrate that in this population of ULD subjects, BRV administered for 16 weeks was [REDACTED] and well tolerated. In addition, the BRV 150mg/day dose appeared to be as well tolerated as the BRV 5mg/day dose and PBO.</p>		
CONCLUSIONS: In conclusion, the study was not able to demonstrate a statistically significant treatment effect of BRV versus PBO on the efficacy endpoints. The small number of subjects, the choice of study design and endpoints, and variability in factors such as disease severity could have contributed to the failure to reach the primary objective in this study.		
Report Date: 07 Oct 2008		

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