2. SYNOPSIS

Name of Sponsor Company: UCB Pharma SA	Individual Study Table Referring to Module	*(For National Authority Use only)*
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Title of Study: A multi-center, 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): Thirteen investigators in 6 countries actively participated in the study.		
Study Center(s): Thirteen sites in 6 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: 21-Nov-2006 Last subject completed: 15-Oct-2007	**Phase of Development:** Therapeutic confirmatory/Phase 3	
Objectives: **Primary Objective** The primary objective of the study was to compare the efficacy of BRV 50mg/day and 150mg/day in bid administration with PBO, on the symptom relief of Action Myoclonus in subjects with ULD. **Secondary Objectives** The secondary objectives were to compare the efficacy of BRV 50mg/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 subjects with ULD. The secondary objectives were also to evaluate the dose/clinical response relationship, to assess the safety and tolerability of BRV in this subject population as well as to assess the effect of BRV on the global evaluation of the disease evolution (assessed by the Investigators) of these ULD subjects. **Exploratory Objectives** The exploratory objectives were to evaluate the effect of BRV on the mood, on the health-related quality of life and on the global evaluation of the evolution of the disease (assessed by the subjects) of these ULD subjects.		

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Methodology:
This was a multi-center, randomized, double-blind, PBO-controlled, parallel study to evaluate the efficacy and safety of BRV at doses of 50mg/day and 150mg/day in bid administration (oral tablets of 25mg, 50mg and matching PBO) as adjunctive treatment in adolescent and adult subjects (≥16 years of age) with genetically ascertained ULD. Subjects were centrally randomized to PBO, BRV 50mg or BRV 150mg in a ratio of 1:1:1. The randomization was stratified for concomitant use of piracetam (PIR) or levetiracetam (LEV). BRV 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 study) or by a Down-titration Period and a 2-week Drug-free Period (for subjects not entering the long-term Follow-up study).

Number of Subjects:
To have 39 completed subjects, it was planned to have 54 subjects screened and 45 subjects randomized, 56 subjects were screened and 50 subjects were randomized.

Diagnosis and Main Criteria for Inclusion:

- Subjects with diagnosed ULD ascertained by appropriate genetic testing for a homozygous or compound heterozygous mutation in the Cystatin B gene.
- Subjects with moderate to severe myoclonus documented by an Action Myoclonus sum score of ≥30 (evaluation by Investigator).
- Subjects currently being 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, 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 currently being or having been treated with valproate up to the maximum recommended daily dose 60mg/kg or serum levels of 100µg/mL or up to their individual optimal dose, or maximum tolerated dose, as specified by the Investigator. The reason for discontinuation or for maintenance at a dose lower than the maximum recommended daily dose has to be specified in the CRF (eg, adverse effect or significant risk thereof, lack or loss of efficacy).
- Concomitant antiepileptic drugs(s) (AED[s]) being stable from at least 1 month before Visit 1 and during the whole study period.
- Male/female subjects from 16 years of age onwards. Subjects under 18 years of age could only be included where legally permitted and ethically accepted.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
Brivaracetam	Oral tablet of 25mg Oral tablet of 50mg	14910 15136/15137

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 the Long-Term Follow-up study).

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Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
Matching PBO tablet	Matching 25mg PBO tablet Matching 50mg PBO tablet	14909 14912/14927

Criteria for Evaluation:

Efficacy:

The primary efficacy variable was the percent reduction from Baseline on the centrally read Action Myoclonus (Section 4 of the Unified Myoclonus Rating Scale [UMRS]) score as assessed at the end of the Treatment Period (Visit 7 or the Early Discontinuation Visit).

The secondary efficacy variables were:

- Percent reduction from Baseline in the centrally-read Functional Disability score (Section 5 of the UMRS)
- Percent reduction from Baseline in the centrally-read Stimulus Sensitivity score (Section 3 of the UMRS)
- Percent reduction from Baseline in the Myoclonus Patient Questionnaire (Section 1 of the UMRS)
- Global Evaluation Scale by Investigator (I-GES)

The exploratory variables were:

- The Patient Quality of Life Inventory in Epilepsy– 31 (QOLIE-31-P) subscales scores (Seizure Worry, Overall Quality of Life, Emotional Well-being, Energy/Fatigue, Cognitive Functioning, Medication Effects and Daily Activities/Social Functioning), the Total score and the Health Status Item score
- The Hospital Anxiety and Depression Scale (HADS) scores (Anxiety and Depression)
- The Patient's Global Evaluation Scale (P-GES)

Safety:

Safety variables included treatment-emergent adverse events (AEs), physical examination assessments, clinical laboratory results (hematology, blood chemistry and urinalysis), electrocardiograms, vital signs (including body weight), plasma BRV levels and plasma antiepileptic drug/antimyoclonic drug levels.

The seizure frequency was assessed for generalized tonic-clonic seizures and for all seizures altogether.

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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.

The efficacy analyses were performed on the intention-to-treat population. In order to control for multiplicity, the first hypothesis for the primary efficacy variable that was tested compared PBO vs the pooled BRV doses. If this hypothesis was rejected (at 5%), both pairwise comparisons of PBO vs each BRV dose were tested at 5%.

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 PBO.

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 per-protocol 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 analysis of covariance (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 Action Myoclonus score (centrally-read) percent reduction from Baseline over the Treatment Period within strata as well as combination of strata was 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 PBO vs 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 (section 5 of the UMRS)
- Stimulus sensitivity (section 3 of the UMRS)

Myoclonus patient questionnaire (section 1 of the UMRS)

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The analysis of the secondary variables was a non-parametric analysis.
The Global Evaluation Scale by Investigator (I-GES) was compared between PBO 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 precipitating factors of myoclonus, and prior and concomitant medication use were similar between the 3 groups. However, the PBO group had lower Baseline Action Myoclonus scores and Functional Disability scores than either BRV treatment group.

For the primary efficacy endpoint, the median percent reduction from Baseline in the centrally-read Action Myoclonus score at the Last Treatment Visit was 26.3% for the BRV 50mg group and 16.9% for the BRV 150mg group as compared to 5.6% for the PBO group in the ITT population. The estimated difference vs PBO was 16.3 for the pooled BRV group, 23.3 for the BRV 50mg group and 9.6 for the BRV 150mg group. The difference vs PBO was not statistically significant for the pooled BRV group and therefore no conclusions about the effect of BRV 50mg or BRV 150mg vs PBO can be drawn.

Despite the absence of statistically significant results on the primary endpoint, at all treatment visits the mean and median values for the percent reduction from Baseline were higher in the BRV 50mg and BRV 150mg groups than in the PBO group. These values were also higher in the BRV 50mg group than in the BRV 150mg group. The results of the per-protocol analysis and the sensitivity analyses were consistent with the primary analysis.

Further testing of the secondary endpoints could only be performed for indicative purposes. The secondary endpoint of I-GES showed a trend towards a beneficial effect of BRV 50mg, but not BRV 150mg, compared to PBO. Results from the Functional Disability score, Stimulus Sensitivity score, and Myoclonus Patient questionnaire did not show any clear differences between the 3 treatment groups.

Several pre-planned exploratory efficacy analyses were performed. QOLIE-31-P and HADS scores at Last Maintenance Visit showed general improvements from Baseline in patient functioning for BRV treated subjects and worsening or lower improvements for PBO treated subjects. The greatest differences favoring BRV over PBO where seen for Cognitive Functioning for the BRV 50mg and BRV 150mg groups, Emotional Well-Being for the BRV 50mg group and the Total QOLIE-31-P score for both BRV groups. Although not consistently, changes from Baseline were generally more favorable to the BRV 50mg group than the BRV 150mg group. The P-GES showed similar favorable trends for the BRV 50mg group.

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SAFETY RESULTS:

There were no clear differences in the AE profile for the 3 treatment groups. The proportion of subjects experiencing at least 1 AE was 56% in the BRV 150mg group as compared to 75% in the BRV 50mg group and PBO group. One subject each in the PBO group and BRV 150mg group permanently discontinued study drug due to an AE. No subjects temporarily discontinued study drug due to an AE or had a dose change due to an AE. The proportion of subjects with drug-related AEs was 19% in the BRV 50mg group and 28% in the BRV 150mg group as compared to 44% in the PBO group.

There were no clear differences in the overall AE profile for the 3 treatment groups between the Up-titration and Maintenance Periods. The number of subjects with at least 1 AE was greatest in the BRV 50mg group and lowest in the BRV 150mg group during the Up-titration Period, greatest in the PBO group and comparable between the 2 BRV groups during the Maintenance Period, and comparable between the 3 treatment groups during the Conversion Period.

"Headache" was reported by 3 subjects each in the PBO and BRV 50mg groups and by 2 subjects in the BRV 150mg group. "Somnolence" was reported by 4 subjects in the PBO group, 2 subjects in the BRV 50mg group and no subjects in the BRV 150mg group. "Dizziness" was reported by 3 subjects in the BRV 50mg group, 1 subject in the BRV 150mg group and no subjects in the PBO group. No other AE was reported by more than 2 subjects in any treatment group. "Somnolence" was the most frequently-reported drug-related AE (4 subjects in the PBO group).

No BRV-treated subject reported an AE of severe intensity. One subject in the BRV 150mg group experienced a treatment-emergent serious adverse event (SAE) ("myoclonus"), which was considered to be of unlikely relationship to study drug, resolved and did not result in a discontinuation or change in study drug dose. No other BRV-treated subject experienced an SAE. Three subjects in the PBO group experienced an SAE. There were no deaths during the study.

No clinically relevant changes from Baseline were observed in any clinical laboratory (hematology and blood chemistry) parameters or vital sign parameters. Few potentially clinically significant clinical laboratory or vital sign parameters were recorded in any of the 3 treatment groups.

There were no trends for increases in seizure frequency per week during treatment with BRV or PBO compared to Baseline.

None of the ECG abnormalities that were observed were clinically significant.

CONCLUSIONS:

In conclusion, the study was not able to demonstrate a statistically significant treatment effect of BRV vs PBO on the efficacy endpoints. The failure to reach the primary objective may have resulted from the small number of subjects, greater than expected variability, the choice of study design and endpoints, differences in Baseline efficacy scores between the PBO vs the 2 BRV treatment groups, and variability in factors such as disease severity. In this study population BRV was [redacted] and well tolerated, and the 150mg/day dose appeared to be as well tolerated as the 50mg/day dose.

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