SP0794, 2005-002814-39

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB BIOSCIENCES, Inc.

(formerly SCHWARZ BIOSCIENCES, Inc.)

8010 Arco Corporate Drive 40789

Raleigh, NC 27617

USA

Official study title:

A multicenter, double-blind, randomized, placebo-controlled, two-arm, parallel-group, sleep lab trial to investigate the efficacy and safety of transdermal rotigotine in subjects with idiopathic restless legs syndrome

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Name of company: SCHWARZ BIOSCIENCES, Inc.	**Individual trial table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of finished product: Not applicable*	**Volume:** Not applicable	
Name of active ingredient: Rotigotine	**Page:** Not applicable	

Title of trial: A multicenter, double-blind, randomized, placebo-controlled, two-arm, parallel-group, sleep lab trial to investigate the efficacy and safety of transdermal rotigotine in subjects with idiopathic restless legs syndrome

Investigators: [redacted]

Trial site(s): Single site

Publication (reference): None

Studied period (years): **First subject enrolled**: 24 Nov 2005 **Last subject completed**: 21 Jul 2006	**Phase of development: 3**

Objectives: The objective of this trial was to demonstrate that rotigotine is effective in subjects with idiopathic RLS based on the Periodic Limb Movement Index (PLMI; PLMs/total time in bed [TIB]) as measured by polysomnography (PSG).

Methodology: SP794 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, 2-arm parallel-group trial in subjects with idiopathic RLS. Subjects were enrolled and randomized to receive placebo or rotigotine in a 2:1 fashion.

A Run-In Period was required for subjects who had previously received RLS therapy or prohibited concomitant medications and to establish homogeneous Baseline conditions for all subjects. Subjects who had had previous treatment with a dopamine agonist completed a Run-In Period of 4 weeks (28 days) prior to Baseline (Visit 2). Sleep lab measurements were performed in the 2 consecutive nights prior to Baseline (Visit 2) and prior to the End of Maintenance (Visit 7). All subjects began the 3-week Titration Period at a daily dosage of rotigotine 2.25mg/placebo. Subjects were up-titrated weekly in 2.25mg/day increments to their optimal dose, with a maximum dose of rotigotine 6.75mg/placebo. The maximum length of titration is 21 days (+3 days), although not all subjects required 21 days to reach their optimal dose. When the Titration Period was complete, or both the subject and investigator decided that the dose was optimal for the subject, the subject remained at that dose and entered the 4-week Maintenance Period. Dose adjustments were not allowed during the Maintenance Period. A 7-day Taper Period was provided to allow for safe, gradual withdrawal from trial medication.

Subjects who completed the 4-week Maintenance Period and Taper Period were eligible to

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

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participate in an open-label extension trial. Subjects who did not complete the 4-week Maintenance Period or who chose not to participate in the open-label extension trial completed a 30-day Safety Follow-Up Period.

Number of subjects (planned and analyzed): Approximately 60 subjects were planned for randomization in this trial, participating at approximately 10 sites. A total of 67 subjects were randomized to receive treatment and 66 were included in the primary analysis.

Diagnosis and main criteria for inclusion: Subjects who met the diagnosis of idiopathic RLS based on the 4 essential clinical features according to the International Restless Legs Syndrome Study Group were allowed to enroll in this trial. In addition In addition, subjects must have (1) either be de novo (ie, had no previous treatment for RLS) or have had initial response to previous dopaminergic treatment, (2) have a score of ≥15 on the International Restless Legs Scale (IRLS) Rating Scale (indicating moderate to severe RLS) at Baseline, (3) have a score of ≥4 points on the Clinical Global Impressions (CGI) Item 1 assessment (indicating moderately ill) at Baseline, and (4) have a Periodic Limb Movement Index (PLMI; periodic limb movements [PLMs]/total time in bed [TIB]) of ≥15 based on polysomnography (PSG) as assessed by the investigator.

Subjects were excluded from the trial if they had secondary RLS; a history of sleep disturbances; other central nervous diseases and any other psychotropic medications; were pregnant; had a QTc interval of ≥500ms at Visit 1, or had an average QTc interval of ≥500ms at Baseline; had symptomatic orthostatic hypotension with a decrease of blood pressure (BP) from supine to standing position of ≥20mmHg in systolic BP or of ≥10mmHg in diastolic BP taken from the 5-minute supine, and 1- and/or 3-minute standing measurements at Screening or Baseline, or supine systolic BP <105mmHg at Baseline.

Test product, dose and mode of administration, batch number: Rotigotine was formulated in 5cm^2, 10cm^2, and 15cm^2 patches, containing 2.25mg/day rotigotine (1mg/24h), 4.5mg/day (2mg/24h), and 6.75mg/day (4mg/24h) respectively. Batch numbers were as follows: 5cm^2 patches, [redacted] 10cm^2 patches, [redacted] and 15cm^2 patches, [redacted]

Duration of treatment: Treatment duration was up to 8 weeks (3-week Titration Period, 4-week Maintenance Period, 1-week Taper Period).

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Reference therapy, dose and mode of administration, batch number: Placebo patches were matched according to size and appearance. Batch numbers were as follows: 5cm^2 patches, [redacted] 10cm^2 patches, [redacted] and 15cm^2 patches, [redacted]

Criteria for evaluation:

Efficacy: The primary efficacy outcome was assessed by the reduction of the PLMI at the end of the Maintenance Period compared to Baseline. PLMI (PLMs/TIB) data was obtained from PSGs. The following secondary variables were measured as change from Baseline at the end of the Maintenance Period: PLMSAI (Periodic Limb Movements during Sleep Arousal Index; PLMs during sleep with arousals/total sleep time), Sleep efficiency (%; sleep time/TIB), IRLS sum score, CGI Item 1 (severity of illness), and MOS Sleep Scale-Adequacy Subscale.

Pharmacokinetics/pharmacodynamics: The pharmacokinetics of rotigotine were assessed by plasma concentration levels of rotigotine and apparent dose measurements.

Safety: The following safety variables were measured: adverse events (AEs) reported spontaneously by the subject or observed by the investigator, changes in laboratory tests (hematology and blood chemistry), changes in vital signs (including orthostatic assessment), physical and neurological examination findings, changes in 12-lead electrocardiograms (ECGs), subject's rating of daytime sleepiness as measured by the Epworth Sleepiness Scale (ESS), changes in menstrual and sexual function, change from Baseline in the Augmentation Severity Rating Scale (ASRS) at the end of the Maintenance Period, changes in the Self-Rating Depression Scale (SDS), Global Subject Rating of Tolerability, and CGI Item 4.

Statistical methods: The primary analysis was an analysis of covariance (ANCOVA) of the log-transformed PLMI at the end of the Maintenance Period. The distribution of the PLMI was expected to be skewed; therefore, a log-transformation was planned for data evaluation.). An ANCOVA was performed to determine treatment effects using log-transformed Baseline PLMI as a covariate and center/region (as appropriate) as a factor to estimate the log-transformed least squares means (LS means) at the end of the Maintenance Period for the PLMI. A standard 1-sided t-test with a 0.025 significance level was performed for the difference of the log-transformed treatment LS means, and (2-sided) p-values and 95% confidence intervals (CI) was provided. Back-transformed treatment LS means and the ratio of the 2 treatments with CI for the ratio (by back-transformation of the LS means differences and CI) were provided.

Appropriate descriptive statistics, including changes from Baseline, were summarized and

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displayed (by visit and other key variables if applicable) for both continuous and categorical variables. Statistics for continuous variables included: n (number of subjects with non-missing values), mean, standard deviation (SD), median, minimum, and maximum. Statistics for categorical variables consisted of the total counts and percentages of subjects falling within each category. In general, summary statistics were presented by treatment group and by maintenance dose for safety analyses.

Summary and conclusions:

Efficacy:

- Superiority of rotigotine over placebo was demonstrated at a significance level of 0.025 for the primary efficacy variable (reduction from Baseline in the PLMI at the end of the Maintenance Period).
- The results of the IRLS sum score (secondary variable) are consistent with the primary analysis. Twenty-six percent (26%) of rotigotine-treated subjects had a score of 0, reflecting they did not have any RLS symptoms at the end of the Maintenance Period.
- The majority of rotigotine-treated subjects (73%) achieved a clinically normal level of ≤2 on the PLMASI (arousal index) compared to 25% of placebo-treated subjects.
- Overall, the efficacy results in this trial were positive with respect to the objective measures (eg, PLMI); non-PLM parameters related to sleep (ie, non-movement secondary efficacy parameters) did not show pronounced changes.

Pharmacokinetics/pharmacodynamics results:

- Mean rotigotine plasma concentrations increased proportionally with dose level. The rotigotine plasma concentrations within a dose group were relatively stable during the Maintenance Period. These data are consistent with results observed in previous trials.
- A mean apparent dose of 39.6% of total drug content was detected, which is consistent with the results from previous trials.
- In this trial, rotigotine had an influence on the change from Baseline in the IRLS sum score. However, there is no clear exposure response relationship.

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Safety results:

- Rotigotine was well tolerated in this trial. Most AEs were consistent with stimulations of dopamine receptors and use of a transdermal patch.
- The most frequently occurring AEs were nausea, headache, and application site reactions.
- All application site reactions were mild or moderate in severity and none led to discontinuation from the trial.
- There were no treatment-emergent SAEs during the trial.
- Overall, 2 rotigotine-treated subjects and 1 placebo-treated subject discontinued from the trial because of an AE.
- Overall, there is no evidence for an association between rotigotine treatment and ECG abnormalities or changes at doses up to 6.75mg/day.
- No clinically relevant changes in vital signs (including orthostatic assessment), clinical chemistry, hematology, endocrine parameters, or urinalysis, physical or neurological examination, or menstrual or sexual function were observed.

Conclusions:

- Superiority of rotigotine over placebo was demonstrated at a significance level of 0.025 for the primary efficacy variable (reduction from Baseline in the PLMI at the end of the Maintenance Period).
- The results of the IRLS sum score (secondary variable) are consistent with the primary analysis. Twenty-six percent (26%) of rotigotine-treated subjects had a score of 0, reflecting they did not have any RLS symptoms at the end of the Maintenance Period.
- The majority of rotigotine-treated subjects (73%) achieved a clinically normal level of ≤2 on the PLMASI (arousal index) compared to 25% of placebo-treated subjects.
- Overall, the efficacy results in this trial were positive with respect to the objective measures (eg, PLMI); non-PLM parameters related to sleep (ie, nonmovement secondary efficacy parameters) did not show pronounced changes.
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