SP0790, 2005-000428-18

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB BIOSCIENCES, Inc.

(formerly SCHWARZ BIOSCIENCES, Inc.)

8010 Arco Corporate Drive

Raleigh, NC 27617

USA

Official study title:

A multi-center, randomized, double-blind, placebo-controlled, four-arm parallel-group trial to investigate the efficacy and safety of three different transdermal doses of rotigotine in subjects with idiopathic restless legs syndrome

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 multi-center, randomized, double-blind, placebo-controlled, four-arm parallel-group trial to investigate the efficacy and safety of three different transdermal doses of rotigotine in subjects with idiopathic restless legs syndrome		
Investigators: This was a multicenter, multinational trial.		
Trial site(s): 49 sites in 8 countries		
Publication (reference): None		
Studied period (years): **First subject enrolled**: 31 May 2005 **Last subject completed**: 23 Aug 2006	**Phase of development:** 3	
Objectives: The primary objective of this trial was to demonstrate efficacy of rotigotine against placebo in subjects with idiopathic restless legs syndrome (RLS) over a 6-month Maintenance Period. The secondary objective was to investigate the safety and tolerability of rotigotine.		
Methodology: SP790 was a Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled, 4-arm, parallel-group trial of rotigotine in subjects with RLS. Subjects were enrolled and randomized to receive placebo, 2.25, 4.5, or 6.75mg/day rotigotine. A 7-day Run-In Period was required for subjects who previously received RLS therapy or prohibited concomitant medications, and to establish homogeneous Baseline conditions for all subjects. Subjects on previous dopamine agonists discontinued therapy for 28 days prior to the Baseline Visit. Subjects taking levodopa discontinued therapy at least 7 days prior to the Baseline Visit. All subjects began the 3-week Titration Period at a daily dosage of 2.25mg rotigotine/placebo. Subjects were up-titrated weekly in 2.25mg/day increments to their assigned daily dose. After the Titration Period was completed, subjects entered the 6-month Maintenance Period. A 7-day Taper Period was provided to allow for safe, gradual withdrawal from trial medication. Subjects who did not complete the 6-month Maintenance Period or who chose not to participate in the open-label extension trial completed a 30-day Safety Follow-Up Period. Subjects who completed the 6-month Maintenance Period and 7-day Taper Period were eligible to participate in an open-label extension trial.		

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

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Number of subjects (planned and analyzed): Approximately 450 subjects were planned for enrollment in this trial. A total of 549 subjects were enrolled in the trial and 458 subjects were randomized to receive treatment.

Diagnosis and main criteria for inclusion: Subjects were included if they were ≥18 and ≤75 years of age; met the diagnosis of idiopathic RLS based on the cardinal clinical features according to the International Restless Legs Syndrome Study Group; had an initial response to previous dopaminergic treatment for RLS or had no previous dopaminergic treatment (ie, de novo); had a score of ≥15 on the International Restless Legs Scale (IRLS; indicating moderate to severe RLS) at Baseline; and scored ≥4 points on the Clinical Global Impressions (CGI) Item 1 assessment (indicating at least moderately ill) at Baseline.

Subjects were excluded from the trial if they had secondary RLS; a history of sleep disturbances; other central nervous diseases (eg, Parkinson's disease); 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 and 10cm^2 patches, containing 2.25mg/day rotigotine (1mg/24h) and 4.5mg/day (2mg/24h), respectively. Assigned doses were achieved by a combination of patches. Batch numbers were as follows—5cm^2 patches: [redacted] 10cm^2 patches: [redacted].

Duration of treatment: Treatment duration was up to 7 months (3-week Titration Period, 6-month Maintenance Period, 1-week Taper Period).

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]

Criteria for evaluation:

Efficacy: The primary efficacy outcome was assessed by the absolute change from Baseline at the end of the Maintenance Period in the IRLS sum score and the CGI Item 1 (severity of

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illness) score. Secondary efficacy variables included IRLS responder (defined as a subject with a decrease of ≥50% in IRLS sum score from Baseline at the end of the Maintenance Period), CGI Item 1 Responder (defined as a subject with a decrease of ≥50% in CGI Item 1 at the end of the Maintenance Period), changes in CGI Items 2 and 3 (continuous) during the Maintenance Period, change from Baseline in RLS-6 Rating Scales at the end of the Maintenance Period, and the Global Subject Rating of Efficacy.

Pharmacokinetics/pharmacodynamics: The pharmacokinetics of rotigotine were assessed by plasma concentration levels of rotigotine and apparent dose measurements (approximately 20% of subjects).

Health outcomes: Health outcomes were assessed by change from Baseline in the RLS-Quality of Life questionnaire at the end of the Maintenance Period and changes in the Work Productivity and Activity Impairment questionnaire at the end of the Maintenance Period.

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, 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 Medical Outcomes Study Sleep Scale score from Baseline at the end of the Maintenance Period, changes in the Self-Rating Depression Scale, Global Subject Rating of Tolerability, CGI Item 4, application site assessment, and patch adhesiveness .

Statistical methods: Treatment with the different rotigotine doses (6.75, 4.5, and 2.25mg/day) were compared to placebo to demonstrate superior efficacy. An analysis of covariance (ANCOVA) was performed for the changes from Baseline to end of the Maintenance Period with dose level or placebo as the main factor, Baseline as a covariate, and center/region/country (if applicable) as a factor. From this ANCOVA, treatment least squares means (with 95% confidence intervals) were calculated and 1-sided 2-sample t-tests were performed (significance level 0.025) to demonstrate superiority of the rotigotine dose level versus placebo, starting with 6.75mg/day. The corresponding p-values were calculated. Significant results (at significance level 0.025) for both coprimary endpoints are required to demonstrate superiority of the rotigotine dose level over placebo. If a level was successful, the next lower dose level was tested

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in a similar fashion, and so forth. Since both primary variables must show statistically significant results to achieve the trial objectives, no sample size adjustment for multiplicity was required.

Appropriate descriptive statistics for secondary efficacy variables, including changes from Baseline, were summarized and 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 nonmissing values), mean, standard deviation, median, minimum, and maximum values. Statistics for categorical variables consisted of the total counts and percentages of subjects falling within each category.

Safety analyses were summarized using the Safety Set. Most analyses were performed by maintenance dose and randomized dose. "Maintenance dose" was defined as the dose at which the subject entered the Maintenance Period. For subjects who withdrew during the Titration Period, the last applied dose was considered the maintenance dose. If a placebo subject was treated with an active dose by error during the course of the trial, the maintenance dose was defined as the lowest active dose the subject ever received.

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Summary and conclusions:

Efficacy: The following conclusions can be drawn based on this analysis:

- Rotigotine is an effective treatment for RLS as monotherapy at doses ranging from 2.25 to 6.75mg/day.
- Superiority over placebo at doses ranging from 2.25 to 6.75mg/day was demonstrated for the coprimary variables (mean change from Baseline in IRLS sum score and CGI Item 1 at the end of the Maintenance Period); improvements in the coprimary variables were clinically relevant in all rotigotine treatment groups.
- Onset of action was observed in the rotigotine treatment groups after Week 1 of the Titration Period (ie, at the first post-Baseline measurement).
- The treatment effect was maintained throughout the 6-month Maintenance Period.
- Approximately one-fourth of rotigotine-treated subjects (24%, 79/333 subjects) were symptom-free (IRLS sum scores=0) at the end of the Maintenance Period compared to 12% of placebo-treated subjects.
- Consistent dose-dependent results were observed across primary and secondary efficacy assessments, with the most pronounced improvement observed in the rotigotine 6.75mg/day treatment group.

Pharmacokinetics/pharmacodynamics results: Rotigotine plasma concentrations increased with dose. 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 41.4% of total drug content was detected.

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: The following conclusions can be drawn from this comprehensive safety analysis:

- Rotigotine was well tolerated in this trial. Most AEs were consistent with stimulation of dopamine receptors and use of a transdermal patch.
- The most frequently occurring AEs were application site reactions, nausea, fatigue, and headache.
- Application site reactions occurred in 42% of rotigotine-treated subjects; 89% of those were mild or moderate in severity.
- The incidence of SAEs was similar across all rotigotine treatment groups, but higher than the placebo group.
- Adverse events leading to discontinuation occurred in 16% of rotigotine-treated subjects compared to 7% of placebo-treated subjects. The majority of AEs in rotigotine-treated subjects that led to discontinuation from the trial occurred during the Maintenance Period.
- 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.
- There is no evidence of augmentation based on the results of the ASRS.

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Conclusions: In summary, the objectives of this trial were met based on the following conclusions:

- Rotigotine is an effective treatment for RLS as monotherapy at doses ranging from 2.25 to 6.75mg/day. Rotigotine was well tolerated in this trial. Most AEs were consistent with stimulation of dopamine receptors and use of a transdermal patch.
- Superiority over placebo at doses ranging from 2.25 to 6.75mg/day was demonstrated for the coprimary variables (mean change from Baseline in IRLS sum score and CGI Item 1 at the end of the Maintenance Period); improvements in the coprimary variables were clinically relevant in all rotigotine treatment groups. Consistent dose-dependent results were observed across primary and secondary efficacy assessments with the most pronounced improvement observed in the rotigotine 6.75mg/day treatment group.
- Onset of action was observed in the rotigotine treatment groups after Week 1 of the Titration Period (ie, at the first post-Baseline measurement). The treatment effect was maintained throughout the 6-month Maintenance Period.
- The most frequently occurring AEs were application site reactions, nausea, fatigue, and headache.
- Application site reactions occurred in 42% of rotigotine-treated subjects; 89% of those were mild or moderate in severity.
- The incidence of SAEs was similar across all rotigotine treatment groups, but higher than the placebo group. Adverse events leading to discontinuation occurred in 16% of rotigotine-treated subjects compared to 7% of placebo-treated subjects. The majority of AEs in rotigotine-treated subjects that led to discontinuation from the trial occurred during the Maintenance Period.
- No clinically relevant changes in vital signs (including orthostatic assessment), ECGs, clinical chemistry, hematology, endocrine parameters, urinalysis, physical or neurological examination, or menstrual or sexual function were observed.

Date of the report: 07 Aug 2007