SP0791, 2005-002611-25

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 GmbH
(formerly SCHWARZ BIOSCIENCES GmbH)
Alfred-Nobel-Str. 10
40789 Monheim
Germany

Official study title:

An open-label extension trial to investigate the safety and tolerability of long-term treatment with transdermal rotigotine in subjects with idiopathic Restless Legs Syndrome

Name of company: SCHWARZ BIOSCIENCES GmbH	**Individual trial table referring to part of the dossier:** Not applicable	*(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: An open-label extension trial to investigate the safety and tolerability of long-term treatment with transdermal rotigotine in subjects with idiopathic Restless Legs Syndrome

Investigators: This was a multicenter, multinational trial.

Trial site(s): 44 sites in 7 [redacted] countries

Publication (reference): None

Studied period (years): 1 **First subject enrolled**: 10 Jan 2006 **Last subject completed**: 08 Sep 2007	**Phase of development: 3**

Objectives: The primary objective of this trial was to assess safety and tolerability of rotigotine in subjects with idiopathic Restless Legs Syndrome (RLS), administered for up to 1 year at an optimal dose. Additionally, data were obtained on changes in severity in RLS symptoms and quality of life under rotigotine treatment during long-term exposure.

Methodology:

SP791 was a multicenter, open-label (OL) extension trial to assess the safety and tolerability of rotigotine in subjects with idiopathic RLS, administered at an optimal dose for up to 1 year in subjects who previously participated in SP790 (6-month pivotal trial) or SP794 (sleep laboratory trial). Subjects who successfully completed the Maintenance Periods and the Taper Periods of SP790 or SP794 were considered eligible to receive treatment in this trial.

All subjects began the trial with a Titration Period of up to 21 (±3) days during which the rotigotine dose was escalated in weekly increments of 2.25mg (5cm^2) from rotigotine 2.25mg/day to a maximum dose of rotigotine 6.75mg/day. After completion of the Titration Period, or upon reaching the subject's optimal dose (defined as absence of or maximal reduction of RLS symptoms without intolerable side effects), the subject remained at that dose and began the 1-year Maintenance Period, during which up- and down-titration of rotigotine dose by steps of 2.25mg (5cm^2) was allowed to maintain a subject's effective dose. Trial participation concluded with a Taper Period of up to 4 days, during which the rotigotine dose was decreased by 2.25mg (5cm^2) every 2 days for safe, gradual withdrawal from trial medication, and a 30-day Safety Follow-Up Period.

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

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Number of subjects (planned and analyzed): Approximately 420 subjects were planned for enrollment in this trial. A total of 341 subjects were enrolled in this trial, and all of these subjects received at least 1 dose of trial medication.

Diagnosis and main criteria for inclusion: Included in this trial were subjects who had completed trial SP790 or SP794 and who had given their written informed consent. Subjects were excluded if they had an ongoing serious adverse event (SAE) that was assessed as related to trial medication by the investigator and/or the sponsor.

Test product, dose and mode of administration, batch number: Rotigotine transdermal patches with the following batch numbers (bulk product batch numbers) were used in this trial:

- 5cm^2 patch containing 2.25mg rotigotine:
- 10cm^2 patch containing 4.5mg rotigotine:
- 15cm^2 patch containing 6.75mg rotigotine:

[redacted]

Duration of treatment: The treatment duration in this trial was approximately 13 months and consisted of a Titration Period of up to 21 days (±3 days), a 1-year Maintenance Period, a Taper Period of up to 4 days, and a Safety Follow-Up Period of 30 days. In fact, the individual Treatment Period including Taper Period amounted to up to 418 days during this trial.

Reference therapy, dose and mode of administration, batch number: None

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Criteria for evaluation:

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, blood chemistry, endocrine measurements, and urinalysis), changes in vital signs (including orthostatic assessment), physical and neurological examination findings, changes in 12-lead electrocardiograms (ECGs), changes in menstrual and sexual function, subject's rating of daytime sleepiness as measured by the Epworth Sleepiness Scale, Global Subject Rating of Tolerability, Clinical Global Impressions (CGI) Item 4, 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), application site assessment, and patch adhesiveness.

Efficacy: The efficacy variables included the absolute change from Baseline at the end of the Maintenance Period in the International Restless Legs Scale (IRLS) sum score and the CGI Item 1 (severity of illness) score, IRLS responder (defined as a subject with a decrease of ≥50% in IRLS sum score from Baseline at the end of the Maintenance Period), IRLS remitter (defined as a subject with an IRLS total score of ≤10 or 0 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, changes in Medical Outcomes Study (MOS) Sleep Scale score from Baseline at the end of the Maintenance Period, and the Global Subject Rating of Efficacy.

Health outcomes: Health outcomes were assessed by **c**hange 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.

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

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Statistical methods:

Descriptive methods were used only for analysis in this OL trial. Safety analyses were summarized using the Safety Set. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) (Version 9.1).

Appropriate descriptive statistics 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 non-missing values), mean, standard deviation, as well as median, minimum, and maximum values. Statistics for categorical variables consisted of the possible categorical outcomes (or collection of outcomes), the total counts, and percentages of subjects falling within each category.

In general, summary statistics were presented by subjects in SP791, subjects from previous double-blind (DB) trial SP790, and subjects from previous DB trial SP794.

Baseline for this OL extension trial was defined as the subjects' Baseline in the previous DB trials SP790 and SP794, respectively.

Summary and conclusions:

<u>Safety results</u>:

In this OL extension trial, subjects were treated with their optimal dose of rotigotine of either 2.25mg/day, 4.5mg/day, or 6.75mg/day for a mean duration of 321 days (ranging from 6 days to 418 days during the Treatment Period including Taper Period). Subjects who started treatment in this OL extension trial had completed the DB trials SP794 and SP790 before, ie, had been randomized to doses of rotigotine or placebo and had been treated with their Maintenance dose for 1 month (SP794) and 6 months (SP790).

Overall, rotigotine was well tolerated during the trial. Most AEs were consistent with stimulation of dopamine receptors and the use of a transdermal patch. The majority of AEs were mild or moderate in intensity. During the trial, the most common AEs were application site reactions, nausea, fatigue, nasopharyngitis, and headache. A total of 16% of subjects withdrew from the trial due to an AE, the most common AEs being application site reactions. Eleven percent of subjects experienced an SAE during treatment and the SAEs occurred across multiple SOCs with no obvious grouping. Two deaths were reported during the trial resulting from multiple cardiac disorders and myocardial infarction, but these AEs

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were considered to be not related to trial medication.

Other significant AEs (application site reactions, sleep attacks) were examined in detail. A total of 111 subjects (33%) reported an application site reaction during the trial. Application site reactions were mild or moderate in 84% of subjects reporting them. Forty-three subjects (13%) withdrew from the trial due to an application site reaction. No application site reaction was an SAE. Isolated events of sleep attacks were reported.

No clinically relevant changes in vital signs were noted.

There was no indication for rotigotine to cause any ECG abnormalities or changes in this trial.

Overall, there was no relevant difference in the incidence of AEs or in laboratory, vital signs, and ECG findings between the subjects who completed SP790 and the subjects who completed SP794 in the previous trial.

Mean ASRS scores were relatively constant throughout the 1-year Maintenance Period.

Efficacy results:

- In this trial, rotigotine was an effective treatment for RLS as monotherapy at doses of 2.25mg/day, 4.5mg/day, and 6.75mg/day. At the end of the Maintenance Period, the majority of subjects (84%) rated the global efficacy of rotigotine as very good or good.
- The majority of subjects (65%) were classified as IRLS responders at the End of the Maintenance Period. The effect at the start of Maintenance was maintained throughout the 1-year Maintenance Period.
- Efficacy of rotigotine was shown using a variety of different subjective assessments. While the majority of subjects reported severe or very severe RLS at Baseline, the majority of subjects reported no or mild RLS at the end of the Maintenance Period. The majority of subjects (81%) improved to a less severe category of RLS during this trial (based on CGI Item 1 analysis) and approximately 80% of subjects rated their change in condition as very much or much improved at the end of the Maintenance Period. The therapeutic effect of rotigotine was rated as very good by approximately 70% of subjects. Efficacy was not only shown for nighttime symptoms, but for daytime symptoms, as well (based on RLS-6 rating scales analysis).

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Health outcomes results:

In general, subjects' quality of life was positively influenced by treatment with rotigotine.

Pharmacology 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.

Conclusions:

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

- Rotigotine was well tolerated in this OL extension trial. In general, AEs were consistent with stimulation of dopamine receptors and use of transdermal patch.
- The most frequently occurring AEs were application site reactions, nausea, fatigue, nasopharyngitis, and headache.
- Application site reactions occurred in 33% of subjects; 84% of those were mild or moderate in intensity.
- Serious adverse events were reported by 11% of subjects. No trends were evident. Adverse events leading to discontinuation of the study occurred in 16% of subjects.
- There were no trends observed in vital signs (including orthostatic assessment), ECGs, clinical chemistry, hematology, endocrine parameters, urinalysis, physical or neurological examination, or menstrual or sexual function.
- The treatment effect that was demonstrated during the DB trials SP790 and SP794 was maintained throughout the 1-year Maintenance Period. Efficacy was evaluated primarily based on the IRLS, CGI Item 1, and RLS-6.

Date of the report: 10 Jul 2008