SP0889, 2006-006752-35

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:

RECOVER – randomized evaluation of the 24-hour coverage: efficacy of rotigotine Phase 3b, multicenter, multinational, double-blind, placebo-controlled, 2-arm trial to evaluate the effect of the 24-hour transdermal delivery of rotigotine on the control of early morning motor function, sleep quality, nocturnal symptoms, and non-motor symptoms in subjects with idiopathic Parkinson's disease

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: Rotigotine transdermal system*	**Volume:** Not applicable	
Name of active ingredient: Rotigotine	**Page:** Not applicable	

Title of trial:

RECOVER – randomized evaluation of the 24-hour coverage: efficacy of rotigotine
Phase 3b, multicenter, multinational, double-blind, placebo-controlled, 2-arm trial to evaluate the effect of the 24-hour transdermal delivery of rotigotine on the control of early morning motor function, sleep quality, nocturnal symptoms, and non-motor symptoms in subjects with idiopathic Parkinson's disease

Investigators: This was a multicenter, multinational trial.

Trial site(s): Forty-nine trial sites in [redacted]

Publication (reference): None

Studied period (years): **First subject enrolled**: 02 May 2007 **Last subject completed**: 09 Mar 2009	**Phase of development:** 3b

Objectives: The objective of this trial was to assess the effects of rotigotine on the control of early morning motor function and sleep disorders compared to placebo in subjects with idiopathic Parkinson's disease. In addition, effects of rotigotine on specific nocturnal and nonmotor symptoms of Parkinson's disease were evaluated.

Methodology:

SP889 was a Phase 3b, multicenter, multinational, double-blind, placebo-controlled, parallel-group, 2-arm trial to evaluate the effect of the 24-hour transdermal delivery of rotigotine on the control of early morning motor function, sleep quality, nocturnal symptoms, and nonmotor symptoms in subjects with idiopathic Parkinson's disease. The trial consisted of a Screening Period (Day -28 to Day -2), Baseline (Day -2, Day -1, and Day 1), a Titration Period (up to 8 weeks), a 4-week Maintenance Period, and a De-Escalation Period (up to 14 days), which was followed by a Safety Follow-Up Visit. During the course of the trial, the manufacturing process for rotigotine was changed. Based on the expiry date and the maximum trial duration for an individual subject, recruitment for SP889 had to be stopped. This allowed all subjects receiving trial medication from the initially approved production process to avoid switching to patches from the new manufacturing process.

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

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Number of subjects (planned and analyzed): A sample size of 336 randomized subjects in a 2:1 ratio (rotigotine:placebo) was necessary to detect a treatment difference in the primary efficacy variables using a two-sample 2-sided t-test with a significance level of 5% and a power of 90%. Based on the enrollment at the time of the recruitment stop, the anticipated number of randomized subjects was reduced, resulting in a decrease in the power of the trial to 84%.

Diagnosis and main criteria for inclusion: Subjects of both genders and ≥18 years of age with early-stage or advanced-stage idiopathic Parkinson's disease (Hoehn and Yahr Stage I-IV), as defined by the cardinal sign, bradykinesia, and at least 1 of the following signs: resting tremor, rigidity, or impairment of postural reflexes were eligible for participation. In addition, the following inclusion criteria applied:

- Subject had unsatisfactory early morning motor impairment
- Subjects taking levodopa (L-DOPA) had to be on a stable dose of L-DOPA (in combination with benserazide or carbidopa) for at least 28 days prior to Baseline.
- Subjects receiving an anticholinergic agent, a monoamine oxidase B inhibitor, or an n-methyl-d-aspartate antagonist had to be on a stable dose for at least 28 days prior to Baseline and had to be maintained on that dose for the duration of the trial.

Test product, dose and mode of administration, batch number: Rotigotine was administered transdermally once daily with a silicone-based patch for a period of 24 hours. Doses were as follows: 2mg/24h, 4mg/24h, 6mg/24h, 8mg/24h, 10mg/24h, 12mg/24h, 14mg/24h, and 16mg/24h. Doses above 8mg/24h were delivered as a combination of suitable patch sizes. Trial medication was dispensed from the following batches: [redacted] ($10cm^2$), [redacted] ($20cm^2$), [redacted] ($30cm^2$), [redacted] ($40cm^2$). For patch sizes above $50cm^2$, the following combinations were used: $50cm^2=20cm^2+30cm^2$, $60cm^2=2x30cm^2$, $70cm^2=30cm^2+40cm^2$, and $80cm^2=2x40cm^2$.

Duration of treatment: The expected maximum duration of the trial per subject was approximately 22 weeks.

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Reference therapy, dose and mode of administration, batch number: Matching placebo patches were administered transdermally once daily with a silicone-based patch for a period of 24 hours. Doses were as follows: 2mg/24h, 4mg/24h, 6mg/24h, 8mg/24h, 10mg/24h, 12mg/24h, 14mg/24h, and 16mg/24h. Doses above 8mg/24h were delivered as a combination of suitable patch sizes. Trial medication (placebo patches) was dispensed from the following batches: [redacted] (10cm²), [redacted] (20cm²), [redacted] (30cm²), [redacted] (40cm²). For patch sizes above 50cm², the following combinations were used: 50cm²=20cm²+30cm², 60cm²=2x30cm², 70cm²=30cm²+40cm², and 80cm²=2x40cm².

Criteria for evaluation:

Efficacy:

The primary efficacy variables included the change from Baseline to the End of Maintenance Period in the early morning Unified Parkinson's Disease Rating Scale (UPDRS) Part III score and in the Parkinson's Disease Sleep Scale (PDSS).

The secondary efficacy variables included the change from Baseline to the End of Maintenance in the Nocturnal Akinesia, Dystonia, and Cramps Score (NADCS) and in the number of nocturias.

The other variables included the change from Baseline to the End of Maintenance in the Parkinson's disease Questionnaire (PDQ-8), the UPDRS Part II (Activities of Daily Living) score, the UPDRS Part IV (Complications of Therapy) score, the Beck Depression Inventory (BDI-II), the Parkinson's Disease Non-Motor Symptom Assessment Scale (PDNMS), and the Likert Pain Scale.

Safety:

Safety was evaluated by the frequency and severity of adverse events (AEs), as reported spontaneously by the subject or observed by the investigator; by the change in vital signs, body weight, electrocardiograms, and clinical laboratory values; and by changes in physical and neurological examination data over the course of the trial.

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Statistical methods: The primary variables were the changes from Baseline at the End of Maintenance in the early morning UPDRS Part III score, and in the PDSS. Analyses of both primary variables were based on the Full Analysis Set (FAS) with last observation carried forward (LOCF). Analyses of covariance were performed for both primary efficacy variables with treatment and (pooled) sites as factors, and Baseline value as covariate. Least square means for treatment effect were calculated and differences between rotigotine (total) and placebo were presented with 95% confidence intervals and p-values. A closed testing procedure was used for the comparison of rotigotine vs placebo for both primary efficacy variables.

All other statistical analyses were performed in a descriptive manner only and were exploratory in nature.

Absolute and relative frequencies of subjects were calculated for categorical variables. Summary statistics, such as mean, standard deviation, median, minimum, and maximum were presented for continuous variables.

Adverse events and diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 9.1. Medication was coded using the WHO-DRL dictionary (Version Q2/2004).

Summary and conclusions:

Efficacy results:

The trial data support the following conclusions regarding the efficacy of rotigotine:

- Rotigotine shows efficacy for the treatment of early-stage and advanced-stage subjects with Parkinson's disease titrated to an optimal dose or a maximal dose of up to 16mg/24h
- Based on the results of UPDRS Part III total score, the treatment with rotigotine led to statistically significant and clinically relevant improvement in subject's early morning motor function at the End of Maintenance.
- Based on the results of PDSS total score, the treatment with rotigotine led to statistically significant and clinically relevant improvement in subject's sleep quality at the End of Maintenance.
- Based on the results of BDI-II, PDNMS, and Likert Pain Scale, improvement of nonmotor symptoms and other parameters, including depression and pain, was demonstrated following treatment with rotigotine.

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Safety results:

In this randomized, placebo-controlled, double-blind trial, subjects were treated with their optimal dose or the maximal dose of rotigotine (ranging from 2mg/24h to 16mg/24h) for a mean duration of 73 days (placebo) and 71 days (rotigotine).

Overall, rotigotine was well tolerated during the trial. Most AEs were consistent with stimulation of dopamine receptors, the use of a transdermal patch, and the clinical picture of the subjects' underlying disease. The majority of AEs were mild or moderate in intensity.

Most subjects completed the trial. The most common reasons for discontinuation were withdrawal of consent and AEs, both evenly distributed across treatment groups.

Incidences of treatment-emergent adverse events were lower during the Maintenance Period than during the Titration Period.

The incidence of serious adverse events (SAEs) was consistent between treatment groups. No SAE occurred in more than 1 subject.

Two deaths in the placebo group were reported resulting from completed suicide and pneumonia aspiration. The investigators assessed the AEs leading to death either as unlikely related or as not related to the intake of trial medication.

Overall, there were few observations in laboratory parameters that were of clinical relevance, most of them occurring in no more than 1 subject.

There were no clinically relevant changes or trends in the mean changes from Baseline to the End of Maintenance Visit for systolic blood pressure, diastolic blood pressure, or pulse rate in either treatment group.

Increases of >60ms in QT interval corrected for heart rate using Bazett's formula (QTcB) were the most frequent changes in post-Baseline parameters for either treatment group.

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Conclusions:

In this adequate and well-controlled trial, rotigotine given at an optimal dose between 2mg/24h to 16mg/24h led to statistically significant and clinically relevant improvement in early morning akinesia and sleep in subjects with idiopathic Parkinson's disease.

The secondary efficacy results indicate that rotigotine treatment improved several other nonmotor symptoms associated with Parkinson's disease, including depression and pain.

Rotigotine was generally well tolerated when titrated up to 16mg/24h in subjects with idiopathic Parkinson's disease.

The most commonly reported AEs were nausea, application and instillation site reactions, dizziness, headache, and dyskinesias, which is consistent with the previously reported AE profile for rotigotine.

Date of the report: 12 Nov 2009