SP0825, 2004-002609-66

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:

A Phase 3, Randomized, Open-Label, Two-arm, Parallel-Group, Multicenter, Multinational Trial to Compare the Efficacy of Rotigotine Transdermal Patch to that of Ropinirole on Early Morning Motor Impairment and Sleep Disorders in Subjects with Early-Stage, 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:*	**Volume:** Not applicable	
Name of active ingredient: Rotigotine	**Page:** Not applicable	

Title of trial: A Phase 3, Randomized, Open-Label, Two-arm, Parallel-Group, Multicenter, Multinational Trial to Compare the Efficacy of Rotigotine Transdermal Patch to that of Ropinirole on Early Morning Motor Impairment and Sleep Disorders in Subjects with Early-Stage, Idiopathic Parkinson's Disease

Investigators: Multicenter trial

Trial site(s): Eleven sites in [redacted]

Publication (reference): Not applicable

Studied period (years):	**Phase of development:**
First subject enrolled: 14 Dec 2004 Last subject completed: 25 Oct 2005	Phase 3

Objectives:

The objective of this trial was to compare the effect of rotigotine and ropinirole on the control of early morning motor impairment and sleep disorders in subjects with early-stage, idiopathic Parkinson’s disease.

Methodology:

This trial was a randomized, open-label, 2-arm, parallel-group, multicenter, multinational trial to compare the efficacy of rotigotine transdermal patch to that of ropinirole on early morning motor impairment and sleep disorders in subjects with early-stage, idiopathic Parkinson’s disease.

Subjects were randomized to receive rotigotine transdermal patch or ropinirole tablets. Each subject was to complete a Screening Period (up to 28 days immediately preceding Baseline), a Baseline Period (including 2 overnight stays), a Titration Period (up to 4 weeks for subjects assigned to rotigotine and up to 6 weeks for subjects assigned to ropinirole), a 4-week Maintenance Period (including 2 overnight stays), and a De-escalation Period (up to 10 days) for subjects who selected not to continue into the open-label extension trial (SP833). After the De-escalation Period, subjects returned for a Safety Follow-Up Visit in 30 days after completion of the Maintenance Period or a Premature Withdrawal Visit.

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

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Number of subjects (planned and analyzed):

A total of 60 subjects were planned for enrollment in order to obtain 40 subjects (20 per arm) for evaluation. Fifty-three subjects were enrolled in the trial, and 51 subjects were randomized. Twenty-five subjects received rotigotine, and 26 subjects received ropinirole. All subjects were included in the safety analyses.

Diagnosis and main criteria for inclusion:

Subjects were male or female at least 18 years of age with early-stage, idiopathic Parkinson's disease (Hoehn & Yahr Stage I-III) ≤5 years in duration with at least 2 or more of the cardinal signs present (bradykinesia, resting tremor, rigidity, or postural instability) and without any other known or suspected cause of Parkinsonism. Subjects were required to have a Unified Parkinson's Disease Rating Scale (UPDRS) Part III (motor examination) Score ≥10 at Baseline. Subjects were required to have unsatisfactory control of early morning motor impairment as determined by the investigator. Subjects receiving an anticholinergic agent (eg, benztropine, trihexyphenidyl, parsitan, procyclidine, biperiden), a monoamine oxidase B (MAO-B) inhibitor (eg, selegiline), or an n-methyl-d-aspartate (NMDA) antagonist (eg, amantadine) must have been on a stable dose for at least 28 days prior to the Baseline Visit and must have been maintained on that dose for the duration of the trial.

Test product, dose and mode of administration, batch number:

Transdermal rotigotine doses included 4.5, 9.0, 13.5, or 18.0mg/day. Rotigotine-treated subjects commenced the Titration Period at 4.5mg/day for 1 week. The rotigotine dose was increased in 4.5mg increments at 7-day intervals until either the optimal dose was identified or the Titration Period was complete and the maximum dose of 18.0mg/day was reached. The optimal dose was defined as the dose at which both the investigator and subject felt that early morning motor impairment was adequately controlled. The subject remained at the optimal/maximum dose throughout the 4-week Maintenance Period. At cessation of therapy, the dose of rotigotine was reduced gradually (by 4.5mg/day every 2 days) over 6 days (depending on maintenance dose level) for those subjects who did not choose to enter the open-label extension trial (SP833).

One rotigotine transdermal patch was applied daily for 24 hours to intact, healthy, and dry skin (free from moisture) of the right or left ventral abdomen, thigh, hip, flank, shoulder, and/or upper arm. Subjects rotated the application site on a daily basis, such that patch application to 1 specific area happened no more than once in a 14-day period.

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Rotigotine patch sizes	**Batch numbers**
10cm^2 containing 4.5mg rotigotine	[redacted]
20cm^2 containing 9.0mg rotigotine	[redacted]
30cm^2 containing 13.5mg rotigotine	[redacted]
40cm^2 containing 18.0mg rotigotine	[redacted]

Duration of treatment:

Excluding the 30-day Safety Follow-Up Visit, the maximal duration of treatment was approximately 9 weeks for rotigotine-treated subjects and 11 weeks for ropinirole-treated subjects, depending on the length of time of the Titration Periods.

Reference therapy, dose and mode of administration, batch number:

Oral ropinirole doses included 0.75, 1.5, 2.25, 3.0, 6.0, or 9.0mg/day. Ropinirole-treated subjects commenced the Titration Period at 0.75mg/day for 1 week. Thereafter, the ropinirole dose was increased at 7-day intervals until either the optimal dose was identified or the Titration Period was completed and the maximum dose of 9.0mg/day was reached. The optimal dose was defined as the dose at which both the investigator and subject felt that early morning motor impairment was adequately controlled. The subject remained at the optimal/maximum dose throughout the 4-week Maintenance Period. At cessation of therapy, the dose of ropinirole was reduced every 2 days over 10 days (depending on maintenance dose level) for those subjects who did not select to enter the open-label extension trial (SP833).

Ropinirole tablets were taken 3 times daily, with or without food.

Ropinirole tablets	**Batch numbers**
0.25mg ropinirole hydrochloride	[redacted]
0.5mg ropinirole hydrochloride	[redacted]
1.0mg ropinirole hydrochloride	[redacted]
2.0mg ropinirole hydrochloride	[redacted]

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Criteria for evaluation:

Efficacy:

Efficacy was evaluated by improvement of early morning motor performance after awakening and before the application of rotigotine or morning dose of ropinirole (UPDRS Part III, Tapping Rate, Standing-Walking-Turning Test, Nocturnal Akinesia Score) improvements in sleep disorders (Parkinson's Disease Sleep Scale [PDSS], Epworth Sleepiness Scale [ESS], Nocturnal Akinesia, Dystonia and Cramps Score [NADCS], number of nocturias); global improvement as rated by investigator (Clinical Global Impression [CGI]) and subject (Patient Global Impression [PGI]); and other assessments (UPDRS Parts I, II, and IV; Parkinson's Disease Questionnaire [short form] [PDQ-8]; and Patient Treatment Preference Scale [PTPS]).

Pharmacokinetics/pharmacodynamics:

Blood samples for pharmacokinetic (PK) analysis were taken at Baseline (inpatient Visit 2), during the Titration Period (Visit 3), the Start of Maintenance (Visit 6), and the End of Maintenance (inpatient Visit 7) and were analyzed by a validated liquid chromatography-mass spectroscopy (LC-MS) assay.

Pharmacodynamic analyses were performed on the overall averages of the Tapping Rate and on the averages of the dominant Parkinson's disease side. Tapping Rate data were collected in the evening and morning at Visit 2 and Visit 7.

Safety:

Safety was evaluated by extent of exposure, adverse event (AE) assessments, clinical laboratory tests, vital sign measurements, weight, physical and neurological examinations, 12-lead electrocardiograms, application site assessment, titration outcome, and assessment of patch adhesiveness.

Statistical methods:

All individual data were listed as measured and with changes from Baseline, where appropriate. All statistical analyses were performed in a descriptive manner. No confirmatory analyses were performed.

Efficacy data are presented for the Completer Set (CS). In order to better understand the effect of rotigotine, the assessment based on the Per Protocol Set (PPS) was considered more relevant for the objectives of this trial; however, the PPS data were identical to the CS

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because no subject had a major protocol deviation. Safety data are presented for the Safety Set (SS).

All psychometric tests/scales were analyzed by its appropriate score, if applicable. If the scale did not support sum scores, individual items were analyzed. Psychometric test/scale scores were regarded as continuous variables and summarized descriptively with summary statistics (n [number of subjects with non-missing values], mean, standard deviation [SD], minimum, median, and maximum) for measured values and changes from Baseline for all visits by treatment group. Analyses of covariance (ANCOVA) were performed for the differences from Baseline to the End of Maintenance with treatment as main factor, Baseline as covariate, and center (defined as appropriate regional/countrywise pooled center groups) as a blocking factor. Least square means for treatment effect was calculated, and the differences between rotigotine and ropinirole treatment least square means were presented with 95% confidence interval (CI). The presentation of CI was regarded as exploratory only. Other continuous variables, like response time, duration, or results of other performance tests, were treated the same way.

For psychometric tests/scales where a score was not well defined, the single items were analyzed using frequency tables with absolute and relative frequencies for all visits by treatment group. For post Baseline visits, shift tables are provided for each visit showing frequency counts (absolute and relative) for each category at Baseline by treatment group. For selected variables, dichotomous responder analyses are provided, showing frequencies (absolute and relative) counting number of subjects by treatment group with improvements to the End of Maintenance compared to Baseline using appropriate responding criteria. Chi-square tests were performed presenting p-values for rotigotine versus ropinirole comparisons descriptively.

All plasma concentration data are listed according to their day and time of collection for each subject. Descriptive summary statistics (n, mean, standard deviation, minimum, median, maximum, n for geometric statistics, geometric mean, and geometric standard deviation) are provided by day, time point, and treatment group for each maintenance dose observed.

Tapping Tests were performed at each time point corresponding to the plasma sample collection. Results are listed individually by treatment group and summarized by descriptive statistics (n, mean standard deviation, minimum, median, and maximum) for measured values and changes from Baseline (defined as last valid measurement before first rotigotine patch application).

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For all quantitative safety variables, summary statistics (n, mean, standard deviation, minimum, median, and maximum) are displayed for all visits, including summary statistics for changes from Baseline, by treatment. For qualitative variables, absolute and relative frequencies are displayed for all visits by treatment. AEs were coded by Medical Dictionary for Regulatory Authorities (MedDRA) v.8.1. Frequency tables are provided showing the number of subjects reporting treatment-emergent AEs (absolute and relative frequencies) by primary System Organ Class and Preferred Term by treatment. Additionally, frequency tables for subjects with treatment-emergent AEs considered as drug-related by the investigator and by intensity are provided by treatment. Pre-treatment AEs are listed.

Summary and conclusions:

Efficacy:

- There were marked improvements in both early morning motor function and sleep disorders. Almost all of the efficacy variables in this trial showed at least slight improvement for both rotigotine-treated subjects and ropinirole-treated subjects. Both treatment groups also showed improvement as rated by the investigator and subject.
- All (100%) rotigotine-treated subjects compared to 9% of ropinirole-treated subjects with previous pharmaceutical treatment experience for Parkinson's disease were "satisfied" or "very satisfied" with the treatment. More of the rotigotine-treated subjects (91%) than ropinirole-treated subjects (60%) "agreed" or "strongly agreed" that they would prefer using a patch over oral medication for treatment of their Parkinson's disease.
- Efficacy results were generally similar between rotigotine and ropinirole.

Pharmacokinetics/pharmacodynamics results:

- Rotigotine plasma concentrations increased in proportion with dose.
- The median ratio of evening to morning C_{ss} was 2.8 for ropinirole and 1.4 for rotigotine.
- The mean apparent dose was approximately 46% of the total drug content.

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Safety results:

- In this trial, rotigotine and ropinirole were well tolerated when administered to subjects diagnosed with early-stage, idiopathic Parkinson's disease when titrated to an optimal dose or the maximal dose of 18.0mg/day.
- The dose titration scheme used in the trial was well tolerated and is, therefore, appropriate for use in subjects with early-stage, idiopathic Parkinson's disease. Most rotigotine-treated subjects (80%) and ropinirole-treated subjects (77%) either achieved their optimal dose or reached the maximum dose during the Titration Period, without back-titration due to an AE.
- During the overall Treatment Period, 14 (56%) of 25 rotigotine-treated subjects and 17 (65%) of 26 ropinirole-treated subjects reported 1 or more AEs. The most common treatment-emergent AEs (ie, those having an incidence ≥5%) for rotigotine-treated subjects included nausea, application and instillation site reactions (application site reaction and application site erythema), fatigue, headache, and dizziness. The most common treatment-emergent AEs for ropinirole-treated subjects included nausea, fatigue, headache, dizziness, and hypertension.
- The most common drug-related treatment-emergent AEs (ie, those judged by the investigator to be at least possibly related to the administration of trial medication) for rotigotine-treated subjects included nausea, application and instillation site reactions (application site reaction and application site erythema), fatigue, and headache. The most common drug-related treatment-emergent AEs for ropinirole-treated subjects included nausea, fatigue, headache, and dizziness. Many of these AEs are consistent with stimulation of dopamine receptors or the use of a transdermal patch system.
- The results indicate that AEs occur at a higher incidence during the initial exposure to rotigotine and ropinirole until the optimal dose is achieved.
- Four (16%) of 25 rotigotine-treated subjects reported an application and instillation site reaction (includes AEs coded as application site reaction or application site erythema). These were mild or moderate in intensity, all were resolved without sequelae, and none were reported as an SAE.

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Conclusions:

- Treatment with the rotigotine transdermal patch resulted in comparable levels of improvement in early morning motor impairment and sleep disorders compared to treatment with ropinirole tablets in subjects who were diagnosed with early-stage, idiopathic Parkinson's disease and who were titrated to an optimal dose of rotigotine up to 18.0mg/day or ropinirole up to 9.0mg/day. Almost all of the efficacy variables in this trial showed at least slight improvement for both rotigotine-treated subjects and ropinirole-treated subjects.
- Rotigotine was generally well tolerated. Most AEs were consistent with stimulation of central dopamine receptors or the use of a transdermal delivery system. Most subjects either achieved their optimal dose or reached the maximum dose during the Titration Period without back-titration due to an AE, the incidence of SAEs was low, and most subjects completed the trial.
- All rotigotine-treated subjects and 9% of ropinirole-treated subjects with previous pharmaceutical treatment experience were "satisfied" or "very satisfied" with the treatment. In addition, more of the rotigotine-treated subjects (91%) than ropinirole-treated subjects (60%) "agreed" or "strongly agreed" that they would prefer using a patch over oral medication for treatment of their Parkinson's disease.

Date of the report: 10 Oct 2006