SP0826, 2004-002598-21

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 3b, Open-Label, Multicenter, Multinational Trial to Evaluate the Effects of Rotigotine Transdermal Patch on Early Morning Motor Impairment and Sleep Disorders in Patients with Idiopathic Parkinson's Disease

Name of company: SCHWARZ BIOSCIENCES, GmbH	**Individual trial table referring to part of the dossier** NA	*(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: A Phase 3b, Open-Label, Multicenter, Multinational Trial to Evaluate the Effects of Rotigotine Transdermal Patch on Early Morning Motor Impairment and Sleep Disorders in Patients with Idiopathic Parkinson's Disease

Investigators: Multicenter trial

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

Publication (reference): Not applicable

Studied period (years): First subject enrolled: 24 Dec 2004 Last subject completed: 21 Jul 2005	**Phase of development:** Phase 3b

Objectives:

The objective of this trial was to assess the effect of rotigotine on the control of early morning motor impairment and sleep disorders in subjects with idiopathic Parkinson's disease. No specific primary or secondary variables were defined for this open-label exploratory trial.

Methodology:

This trial was an open-label, multicenter, multinational trial to evaluate the effects of the rotigotine transdermal patch on early morning motor impairment and sleep disorders in subjects with idiopathic Parkinson's Disease.

Each subject was to complete a Screening Phase (within 28 days before the start of trial medication), a Baseline Phase (including 2 overnight stays), a Titration Phase (up to 8 weeks), a 4-week Maintenance Phase (including 2 overnight stays at the end of Maintenance), and a De-escalation Phase (up to 14 days) (for subjects who selected not to continue into the open-label extension [SP833]). After the De-escalation Phase, subjects returned for a Safety Follow-Up Visit in 30 days.

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

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Number of subjects (planned and analyzed):

A total of 50 subjects were planned for enrollment in order to obtain 40 subjects for evaluation. Fifty-eight subjects were enrolled in the trial. Fifty-four subjects received treatment with the rotigotine and are included in the safety analyses.

Diagnosis and main criteria for inclusion:

Subjects were male or female ages 18 to 85 years, inclusive, with idiopathic Parkinson's disease (Hoehn & Yahr Stage I-IV) as defined by the cardinal sign, bradykinesia, and at least 1 of the following: resting tremor, rigidity, or impairment of postural reflexes. A subject was required to have unsatisfactory control of early morning motor impairment as determined by the investigator. If a subject was taking levodopa with or without Catechol-O-methyl transferase (COMT) inhibitors, he/she must have been on a stable dose of levodopa (in combination with benserazide or carbidopa) with or without COMT inhibitors for at least 28 days prior to Baseline. If the subject was 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), he/she 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, 18.0, 22.5, 27.0, 31.5, or 36.0mg/day. All subjects commenced the Titration Phase at a daily dose of 4.5mg for 1 week. Thereafter, the dose was increased at 7-day intervals in 4.5mg increments until either the optimal dose was identified or the Titration Phase was complete and the maximum daily dose of 36.0mg 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 Phase. At cessation of therapy, the dose of rotigotine was reduced gradually (by 4.5mg/day every 2 days) over 14 days (depending on maintenance dose level) for those subjects who did not select to enter the open-label extension.

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,

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and/or upper arm. Subjects were to rotate the location of each patch on a daily basis such that application of the patch to one specific area happened no more than once in a 14-day period.

Patch sizes (apparent dose)	Batch numbers
10cm^2 containing 4.5mg rotigotine (2mg/24h)	[redacted]
20cm^2 containing 9.0mg rotigotine (4mg/24h)	[redacted]
30cm^2 containing 13.5mg rotigotine (6mg/24h)	[redacted]
40cm^2 containing 18.0mg rotigotine (8mg/24h)	[redacted]

Duration of treatment:

Excluding the 30-day Safety Follow-Up Visit, the maximal duration of treatment per subject was approximately 18 weeks, depending on the length of time of the Screening and Titration Phases.

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

All subjects received rotigotine.

Criteria for evaluation:

Efficacy: Due to the exploratory nature of this trial, no primary or secondary efficacy variables were specified. Efficacy data were analyzed descriptively. Efficacy was evaluated by the Unified Parkinson's Disease Rating Scale (UPDRS), average Tapping Rate, Standing-Walking-Turning Test, Nocturnal Akinesia Score, Parkinson's Disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), Nocturnal Akinesia, Dystonia and Cramps Score (NADCS), number of nocturias, Clinical Global Impression (CGI), Patient Global Impression (PGI), Parkinson's Disease Questionnaire (short form) (PDQ-8), and Patient Treatment Preference Scale (PTPS).

Pharmacokinetics/pharmacodynamics: Blood samples for PK analysis were taken at Baseline (inpatient Visit 2), during titration Weeks 2 and 4 (Visits 3 and 4, respectively), and at the End of Maintenance (inpatient Visit 7) and were analyzed by a validated liquid chromatography–mass spectroscopy (LC-MS) assay. Plasma concentrations at specific time

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points were analyzed descriptively. The calculated time after patch application of the plasma concentration assessment is provided in the data listings and summarized by descriptive statistics. The change in plasma concentration (morning-evening) was calculated using the inpatient plasma concentrations of Visit 7 (End of Maintenance): $\Delta_{Css} = C_{morning} - C_{evening}$.

Pharmacodynamic analyses were performed on the overall averages of the Tapping Rate and on the averages of the primary disease side of the Tapping Rate. Tapping Rate data were collected in the evening and morning at Visit 2 (Baseline) and Visit 7, and Δ_{Css} was analyzed. Pearson's coefficient of correlation was computed for plasma concentrations and changes from Baseline in tapping tests over all time points of collection.

Safety: No safety endpoints were specified. Safety data were analyzed descriptively. Safety was evaluated by AE assessments, clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms, physical and neurological examinations, extent of exposure, weight, assessment of patch adhesiveness, and application site assessment. Blood samples for pharmacokinetic (PK) analysis were taken at Baseline, Visits 3, 4, and 7 (End of Maintenance). A Safety Follow-Up Visit was conducted in 30 days after last dose.

Statistical methods: Due to the exploratory nature of this trial, there was not a specified primary or secondary variable for analysis.

All individual data were listed as measured and with changes from Baseline, where appropriate. All statistical summaries were performed using SAS® Version 9.1 or higher (SAS, SAS-Institute, Cary, NC, USA) using validated program code according to Schwarz Biosciences' SOPs or authorized CRO SOPs. All statistical analyses were performed in a descriptive manner. No confirmatory analyses were done.

Appropriate descriptive statistics were computed and displayed (by visit and other key variables if applicable) for both continuous and categorical variables. Statistics for continuous variables include: n (number of subjects with non-missing values), mean, standard deviation, as well as median, minimum, and maximum. Statistics for categorical variables consist of listing out the possible categorical outcomes (or collections of categories) and then providing the total counts and percentages of subjects falling within them.

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Conclusions:

- In this open-label trial, treatment with transdermal rotigotine improved early morning motor impairment and sleep disorders in subjects who were diagnosed with idiopathic Parkinson's disease and who were titrated to an optimal dose of rotigotine up to 36.0mg/day. In addition, the CGI, PGI, and PDQ-8 showed consistent improvement.
- Subjects experienced improved control of motor performance as supported by improvements in Tapping Rates, UPDRS Part III Score, Nocturnal Akinesia Score, and the Standing-Walking-Turning Test.
- The mean changes between average evening Tapping Rates, average morning Tapping Rates, and the difference between morning and evening average Tapping Rates at the End of Maintenance compared to Baseline for the average of both sides and the dominant affected side showed improvement in motor performance.
- Subjects experienced improved control of sleep disorders as supported by decreased nocturnal akinesia (Nocturnal Akinesia Score, NADCS Sum Score), decreased nocturnal dystonia (Nocturnal Dystonia Score, NADCS Sum Score), decreased nocturnal cramps (Nocturnal Cramps Score, NADCS Sum Score), fewer nocturias, and improved sleep and nocturnal disability (PDSS Sum Score).
- Subjects also experienced improved sleep without daytime somnolence, as supported by a decrease in the ESS Score.
- Based on the Patient Treatment Preference Scale, subjects preferred treatment with the rotigotine transdermal patch compared to previous oral medications.
- Rotigotine was generally well tolerated. Most AEs were consistent with stimulation of central dopamine receptors or the use of a transdermal delivery system. The majority of subjects either achieved their optimal dose or reached the maximum dose during the Titration Period. The incidence of SAEs was low and most subjects completed the trial.

Date of the report: 4 May 2006