SP0833, 2004-002641-12

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 multicenter, multinational, Phase 3b, open-label extension trial to assess the safety and tolerability of long-term treatment of rotigotine patch 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: A multicenter, multinational, Phase 3b, open-label extension trial to assess the safety and tolerability of long-term treatment of rotigotine patch in subjects with idiopathic Parkinson's disease		
Investigators: This was a multicenter, multinational trial with 26 investigators.		
Trial site(s): Twenty-six sites in 8 countries.		
Publication (reference): None		
Studied period (years): 3.5 years **First subject enrolled**: 17 Feb 2005 **Last subject completed**: 11 Dec 2008	**Phase of development:** Phase 3b	
Objectives: The objective of the trial was to assess the safety and tolerability of long-term treatment of rotigotine in subjects with idiopathic Parkinson's disease.		
Methodology: The trial provided subjects who had completed Maintenance Period trials SP824, SP825, and SP826 and who met the eligibility criteria the option of long-term treatment with rotigotine. All subjects in SP824 and SP826 as well as subjects assigned to rotigotine transdermal patch in SP825 entered directly into the Maintenance Period of this open-label extension trial. Subjects assigned to ropinirole in SP825 were de-escalated from ropinirole and entered the Titration Period of SP833 before proceeding into the Maintenance Period. The trial consisted of a Titration Period of up to 8 weeks for subjects previously on ropinirole in SP825, a Maintenance Period of an extended period of time (which lasted until rotigotine became commercially available or the sponsor closed the trial, whichever came first), a De-escalation Period (up to 14 days) for subjects who completed the End of Treatment Visit, and a Safety Follow Up (SFU) Visit 30 days after final administration of trial medication. Subjects returned to the clinic every 3 months until the end of treatment.		

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

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Subjects formerly in SP825 requiring titration on rotigotine commenced dosing in this trial at a dose of 2mg/24h for 1 week. Thereafter, the dose was increased by 2mg/24h increments (every 7±3 days) until the optimal or maximum dose was reached (up to 16mg/24h). Subjects returned to the clinic every other week during the Titration Period, with telephone contacts during weeks when no clinic visit was scheduled. Once a subject from SP825 completed titration and had reached the optimal or maximum dose of rotigotine in the Titration Period, the subject entered the Maintenance Period (Visit M1). Subjects returned to the clinic 1 month later (Visit M1a) to confirm their optimal dose, 2 months later (Visit 2), and then at 3 month intervals until the end of treatment. Subjects continued rotigotine treatment until rotigotine was commercially available or the sponsor closed the trial, whichever came first.

Number of subjects (planned and analyzed): A total of 186 subjects were enrolled in the trial.

Diagnosis and main criteria for inclusion: Included in this trial were subjects who had completed SP824, SP825, or SP826 and who, in the opinion of the investigator, would benefit from long-term treatment with rotigotine. Subjects who had an ongoing serious adverse event that was assessed by the investigator to be related to the trial medication were excluded.

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Test product, dose and mode of administration, batch number: Rotigotine 2, 4, 6, 8, 10, 12, 14, or 16mg/24h via transdermal patch(es). Doses greater than 8mg/24h were administered using a combination of multiple patches.

10cm^2 patch containing 2mg/24h rotigotine: [redacted];

20cm^2 patch containing 4mg/24h rotigotine: [redacted]

30cm^2 patch containing 6mg/24h rotigotine: [redacted]

40cm^2 patch containing 8mg/24h rotigotine: [redacted]

50cm^2 patch(es) containing 10mg/24h rotigotine: [redacted]

60cm^2 patch(es) containing 12mg/24h rotigotine: [redacted]

80cm^2 patch(es) containing 14mg/24h rotigotine: [redacted]

Duration of treatment: Subjects were treated with rotigotine (ranging from 2mg/24h to 16mg/24h) for a mean duration of 658 days (ranging from 8 to 1365 days)

Reference therapy, dose and mode of administration, batch number: Not applicable

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Criteria for evaluation:

Safety variables:

- Adverse events (AEs), as reported spontaneously by the subject or observed by the investigator during the course of the trial
    - Modified Minnesota Impulsive Disorders Interview (mMIDI)
- Change in clinical laboratory values during the course of the trial
- Change in physical and neurological examination data during the course of the trial
- Change in vital signs, body weight, and electrocardiograms (ECGs) during the course of the trial
- Change in Epworth sleepiness scale (ESS) scores during the course of the trial
- Patch adhesiveness

Efficacy variables:

- Change from Baseline in Unified Parkinson's Disease Rating Scale (UPDRS) Part I scores during the course of the trial
- Change from Baseline in UPDRS Part II scores during the course of the trial
- Change from Baseline in UPDRS Part III scores during the course of the trial
- Change from Baseline in UPDRS Part IV scores during the course of the trial
- Clinical Global Impression (CGI) during the course of the trial
- Patient Global Impression (PGI) during the course of the trial
- Change from pretreatment in Hoehn and Yahr stage over the course of the trial
- Rating of patch application site preference and satisfaction with trial treatment, as assessed by a patient treatment preference scale

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Statistical methods: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA®) (Version 9.1). Prior and concomitant medications were coded using the World Health Organization Drug Dictionary, version 2Q/2004.
Appropriate descriptive statistics were computed and displayed (by timepoint, if applicable) for both continuous and categorical variables. Baseline for this open-label extension trial was defined as the subject's Baseline in SP824, SP825, or SP826.

Summary and conclusions:

Safety results: Overall, rotigotine was generally 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. The most common AEs were somnolence, oedema peripheral, and fall. A total of 26% of subjects withdrew from the trial due to an AE, the most common AE leading to discontinuation being application and instillation site reactions (high level term [HLT]). Twenty-four percent of subjects experienced at least 1 serious adverse event (SAE), and the SAEs occurred across multiple system organ classes (SOCs) with no obvious grouping.

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Four deaths were reported resulting from septic shock, suicide, colon cancer, and aspiration pneumonia. All of the deaths occurred after treatment with rotigotine had been discontinued (6 days, 14 days, 20 days, and 99 days posttreatment). The investigators assessed all AEs leading to death as unlikely or not related to the trial medication. Given the comorbidity and the age of the subjects as well as the approximate 3.5-year duration of the trial, the spectrum of AEs leading to death during this trial was not unexpected.

A total of 23 AEs (in 15 subjects) indicative of impulsive-compulsive behavior were recorded during the trial; 11 of these AEs (in 9 subjects) were assessed by the investigators as being at least probably related to the trial medication.

Adverse events regarding application and instillation site reactions were examined in detail. A total of 38 subjects (20%) reported at least 1 treatment-emergent application and instillation site reaction during the trial. One of these application and instillation site reactions (AISRs) was severe in intensity, and none were considered serious in nature. Twelve subjects (7%; reporting a total of 12 AISRs) withdrew from the trial due to these AEs.

Overall, there were no mean changes in laboratory parameters that were of clinical relevance.

For systolic blood pressure, diastolic blood pressure, and pulse rate, there were no clinically relevant changes or trends in the mean changes from Baseline to the End of Maintenance (EoM) Visit. There was no indication for rotigotine to cause any ECG abnormalities or changes in this trial. Changes in QT values were not clinically relevant.

In general, from Baseline to the EoM Visit, there were no increases or decreases in mean QT interval corrected for heart rate by Bazett's formula (QTcB) or QT interval corrected for heart rate by Fridericia's formula (QTcF) values that exceeded 10ms.

The ESS total score increased from 8.7 at Baseline to 10.3 by Visit 14 (first visit after the end of year 3).

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Efficacy results:

As expected, the subjects' Parkinson's disease worsened until the EoM (ie, up to period of approximately 3.5 years). However, at the EoM, the mean change in total scores for UPDRS Part II and III indicated improvement over the Baseline values.

Throughout the Maintenance Period, subjects benefited from treatment with rotigotine regarding handwriting, tremor, and sensory complaints related to parkinsonism. At the EoM, 39% of subjects were defined as responders, meaning that they had a decrease of 20% or more in their total UPDRS sum score (Part II and III) compared with Baseline.

Based on CGI analyses, there was little change in subjects' severity of Parkinson's disease throughout the OL treatment with rotigotine. At the end of OL treatment, only 4% of subjects reported having side effects that outweighed the therapeutic effect of rotigotine.

Conclusions:

- Rotigotine was generally well tolerated in this OL extension trial. In general, AEs were consistent with stimulation of dopamine receptors, the use of a transdermal patch, and complications connected to the subjects' underlying disease.
- The most frequently reported AEs were somnolence, oedema peripheral, and fall.
- Only 1 of all treatment-emergent application and instillation site reactions (HLT) reported throughout this OL trial was severe in intensity, and none were considered serious in nature.
- Serious AEs occurred without any grouping to specific SOCs.
- Overall, there were no mean observations in laboratory parameters that were of clinical relevance. Furthermore, the incidences of vital sign outliers were not clinically relevant throughout the trial.
- Based on UPDRS results, as expected, the subjects' Parkinson's disease progressed over the course of the study (ie, up to period of approximately 3.5 years), but remained improved relative to Baseline.
- Although there was a slight increase in subjects' severity of Parkinson's disease throughout SP833, only 4% subjects reported having side effects that outweighed the therapeutic effect of rotigotine.

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