SP0516, 2004-000148-26

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, Inc.

(formerly SCHWARZ BIOSCIENCES, Inc.)

8010 Arco Corporate Drive

Raleigh, NC 27617

USA

Official study title:

A multi-center, multinational, Phase 3, open-label extension trial to assess the safety of long-term treatment of rotigotine patch in subjects with advanced stage, idiopathic Parkinson's disease who are not well controlled on levodopa

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

Title of trial: A multi-center, multinational, Phase 3, open-label extension trial to assess the safety of long-term treatment of rotigotine patch in subjects with advanced-stage, idiopathic Parkinson's disease who are not well controlled on levodopa

Investigators: This was a multi-center, multinational trial.

Trial site(s): Sixty-three sites (in [redacted])

Publication (reference): None

Studied period (years): Up to 5 **First subject enrolled**: 30 Aug 2004 **Last subject completed**: 19 Dec 2008	**Phase of development:** Phase 3

Objectives: The objective of this trial was to assess the safety and tolerability of long-term treatment of rotigotine in subjects with idiopathic Parkinson's disease.

Methodology: This trial was a single-arm, open-label (OL) extension of the double-blind (DB) trial, SP515. Subjects who had completed 4 months of maintenance in SP515 were eligible to enroll in this extension trial. Before entering SP516, subjects de-escalated from their optimal dose level in SP515. After de-escalation was complete, all subjects started treatment with rotigotine at a dose level of 4mg/24h. The rotigotine dose could be uptitrated to the optimal dose every 7±3 days by 2mg/24h increments up to a maximum dose of 16mg/24h. The Maintenance Period began when the Titration Period was complete, or when both the subject and the investigator decided that an optimal dose had been reached; the maximum length of the Titration Period was 49±21 days. If necessary, a subject's dose of rotigotine could be increased or decreased as needed by the investigator to maintain a subject's effective dose during the Maintenance Period. In case a subject's Parkinson's disease symptoms progressed, increase of the rotigotine dose to the next higher dose was encouraged, up to the maximal dose of 16mg/24h, prior to adding or altering adjunctive anti-Parkinson medications. Subjects continued rotigotine treatment in the Maintenance Period for up to 5 years or until the sponsor closed the trial, whichever came first. At cessation of therapy, the dose of rotigotine was reduced gradually in a De-escalation Period. Depending upon the subject's dose during the Maintenance Period, dose de-escalation

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

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occurred in 2mg/24h steps every 2 days until the subject reached the lowest dose (4mg/24h) and had taken that dose for 2 days. De-escalation could last for up to 12 days depending upon the subject's maintenance dose. The subject was asked to return to the clinic for a SFU Visit 28 days after the End of Treatment Visit.

Number of subjects (planned and analyzed): This was an OL extension trial for subjects who had completed 4 months of DB maintenance therapy in SP515 to give them the option of long-term treatment with rotigotine. Therefore, no formal sample size determination was performed.

It was assumed that approximately 85% of the subjects would complete the 4 months of DB maintenance in SP515. Of these subjects, it was expected that about 90% would enter the OL extension. A total of 395 subjects entered SP516 and were included in the Enrolled Set (ES) and the Safety Set (SS).

Diagnosis and main criteria for inclusion: Subjects with advanced-stage, idiopathic Parkinson's disease who had completed 4 months of maintenance treatment in the DB trial, SP515, and who did not have an ongoing serious adverse event (SAE) that was assessed as related to trial medication were eligible to enter SP516.

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 and patch sizes were as follows: rotigotine 4mg/24h ($20cm^2$), 6mg/24h ($30cm^2$), and 8mg/24h ($40cm^2$). Doses greater than 8mg/24h (ie, 10mg/24h, 12mg/24h, 14mg/24h, and 16mg/24h) were administered using a combination of multiple patches.

Trial medication was dispensed from the following batches:

$20cm^2$: [redacted]

$30cm^2$: [redacted]

$40cm^2$: [redacted]

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Duration of treatment: The planned duration of the trial per subject was until completion of a Maintenance Period of up to 5 years or until the sponsor closed the trial, whichever came first.		
Reference therapy, dose and mode of administration, batch number: Not applicable		

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Criteria for evaluation:

The following variables and analyses were originally defined for SP516:

- Adverse events (AEs), as reported spontaneously by the subject or observed by the investigator recorded over the course of the trial
  - Modified Minnesota Impulsive Disorders Interview
- Change from Baseline in the vital signs, body weight, electrocardiograms (ECGs), clinical laboratory values, and Epworth Sleepiness Scale (ESS) scores over the course of the trial
- Changes from Baseline in physical and neurological examination data over the course of the trial
- Change from Baseline in Unified Parkinson's Disease Rating Scale (UPDRS) scores Part II over the course of the trial
- Change from Baseline in UPDRS scores Part III over the course of the trial
- Change from Baseline in UPDRS scores Part IV over the course of the trial
- Change from Baseline in the sum of UPDRS scores Parts II + III over the course of the trial
- Change from Baseline in the sum of UPDRS scores Parts II, III, and IV over the course of the trial
- Clinical Global Impressions during the course of the trial
- Change from pretreatment in Hoehn and Yahr stage over the course of the trial
- Change in quality of life, from Baseline to end of the trial, as assessed using the Parkinson's Disease Questionnaire 39 Item (PDQ-39)
- Change in quality of sleep, from Baseline to end of the trial, as assessed using the Parkinson's Disease Sleep Scale (PDSS)
- Plasma levels of rotigotine (in approximately 20% of the trial population) over the course of the trial

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Statistical methods: As the primary focus of this trial was on long-term safety, the primary safety variables, including AEs, laboratory parameters, physical and neurological examinations, 12-lead ECGs, vital signs, and ESS values were analyzed descriptively.

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

A "dose of longest duration" during SP516 was allocated to all subjects for the analysis period. For subjects who had more than 1 dose of longest duration in the analysis period (ie, ties), the minimum dose was used. Similarly, if the "dose of longest duration" was 0mg, but the subject was exposed at least once to rotigotine during SP516, the minimum rotigotine dose was utilized. Subjects were grouped by dose in analysis displays based on the dose of longest duration subjects received during the entire SP516 trial.

Baseline for SP516 was defined as SP515 Visit 2 for most assessments or the last SP515 assessment before treatment (eg, laboratory assessments). Baseline for UPDRS Part IV was defined as SP516 Visit 1, and Baseline for Hoehn and Yahr score was defined as SP515 Visit 1.

Adverse events and diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA®, Version 9.1). Concomitant and previous medications were coded using the World Health Organization-Drug Reference List (WHO-DRL, 2Q/2004). All coding was performed prior to database lock.

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Summary and conclusions:

Safety results:

In this OL extension trial, subjects were treated with rotigotine (ranging from 4mg/24h to 16mg/24h) for a mean duration of 858 days (ranging from 1 to 1520 days).

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, application and instillation site reactions (high level term [HLT]), fall, and Parkinson's disease. Investigator reported terms, including worsening or deterioration, were coded to the preferred term of Parkinson's disease. A total of 20% of subjects withdrew from the trial due to an AE, the most common AEs leading to discontinuation being application and instillation site reactions (HLT). Thirty-eight percent of subjects reported at least 1 SAE, and the SAEs occurred across multiple system organ classes (SOCs) with no obvious grouping.

Fifteen deaths were reported (one of which was 4 days post-treatment), resulting from bronchial carcinoma (2 subjects), Parkinson's disease, cerebrovascular accident, cardiac failure, pneumonia, loss of consciousness, narcotic intoxication, sepsis, myocardial infarction, cerebral haemorrhage, intestinal obstruction, and pulmonary embolism (all 1 subject each). One subject who died had respiratory failure and cardiovascular insufficiency, and another had both colon neoplasm and metastatic neoplasm. Except 1 AE of myocardial infarction, where causality was assessed as possibly related by the investigator, all other AEs leading to death were assessed either as unlikely related or not related to the trial medication. Given the comorbidity and the age of the subjects, as well as the long duration of the trial, the spectrum of AEs leading to death during this trial is not unexpected.

A total of 42 AEs (in 22 subjects, 6%) indicative of impulsive-compulsive behavior were recorded during the trial, 25 of which (in 16 subjects) were assessed by the investigators as being at least probably related to the trial medication.

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Adverse events of application and instillation site reactions (HLT) were examined in detail. A total of 103 subjects (26%) reported at least 1 treatment-emergent application and instillation site reaction during the trial. Seven of the application and instillation site reactions were severe in intensity, and 2 were serious in nature. A total of 14 subjects (4%) discontinued prematurely due to these reactions.

Overall, there were no mean changes in laboratory parameters that were of clinical relevance. Individual changes of clinical relevance in hematocrit and hemoglobin were observed in a few subjects.

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). There was no indication for rotigotine to cause any ECG abnormalities. Overall, the majority of subjects (75% to 99% of subjects across all visits) had a QT interval corrected for heart rate by Bazett's formula or QT interval corrected for heart rate by Fridericia's formula classified as <450ms, and had a change from Baseline <30ms (75% to 96% of subjects across all visits).

The ESS total score increased from 7.1 at Baseline to 8.3 at Visit 25 (end of Year 4). Epworth Sleepiness Scale total scores of less than 10 are below the cutoff for excessive daytime somnolence.

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Efficacy results:

Based on UPDRS results, OL treatment with rotigotine led to a general improvement in subjects' ability to cope with activities of daily living (UPDRS Part II) and motor function (UPDRS Part III) during the Titration Period. As expected, the subjects' Parkinson's disease then worsened until the EoM (ie, over a period of approximately 4 years). At the EoM, the mean score for UPDRS Part III was improved over the Baseline value.

Throughout the Maintenance Period, subjects benefited from treatment with rotigotine regarding tremor, sensory complaints related to parkinsonism, and cutting food and handling utensils. Many of the individual item scores for UPDRS Part III improved from Baseline to the EoM. At the EoM, 39% of subjects could still be defined as responders, meaning that they had a decrease of 20% or more in their total UPDRS sum score (Part II + III) compared to Baseline.

Based on CGI analyses, the mean score was the same at Baseline and the End of Treatment, indicating no change in subjects' severity of Parkinson's disease throughout the OL treatment with rotigotine.

At the end of OL treatment, 3% of subjects reported having side effects that outweighed the therapeutic effect of rotigotine.

Pharmacokinetics/pharmacodynamics results:

The results of rotigotine plasma concentration measurements (ie, mean concentrations and variability based on rotigotine doses of 4, 6, 8, 10, 12, 14, and 16mg/24h) are consistent with results observed in other trials. Results gained for the Maintenance Period illustrate a stable plasma level of rotigotine during long-term administration (ie, up to 1 year of repeated dosing).

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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, application and instillation site reactions (HLT), fall, and Parkinson's disease. The majority of AEs were mild or moderate in intensity.
- Serious AEs occurred without any grouping to a specific SOC.
- Overall, there were no mean changes 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, OL treatment with rotigotine led to a general improvement in subjects' ability to cope with activities of daily living and motor function during the Titration Period. As expected, the subjects' Parkinson's disease progressed over the course of the study (ie, over a period of approximately 4 years), but remained improved relative to Baseline.
- Rotigotine plasma concentrations showed a dose proportionality for doses ranging from 4mg/24h to 16mg/24h.
- Rotigotine plasma concentrations remained stable during long-term (up to 1 year) administration.
- Although there was a slight increase in subjects' severity of Parkinson's disease throughout SP516, only 3% of subjects reported having side effects that outweighed the therapeutic effect of rotigotine.

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