SP0824, 2004-002650-59

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, Inc.

(formerly SCHWARZ BIOSCIENCES GmbH)

1950 Lake Park Drive Smyrna, GA 30080

USA

Official study title:

A Phase 3b, Open-label, Multicenter, Multinational Trial to Assess the Tolerability of Switching Subjects from Ropinirole, Pramipexole or Cabergoline to the Rotigotine Transdermal System and its Effect on Symptoms in Subjects with Idiopathic Parkinson's Disease

Name of company: SCHWARZ BIOSCIENCES, Inc.	**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 Assess the Tolerability of Switching Subjects from Ropinirole, Pramipexole or Cabergoline to the Rotigotine Transdermal System and its Effect on Symptoms in Subjects with Idiopathic Parkinson's Disease		
Investigators: Multicenter trial		
Trial site(s): Nine sites in the [redacted] and 3 sites in the [redacted]		
Publication (reference): Not applicable		
Studied period (years): First subject enrolled: 21 Dec 2004 Last subject completed: 11 Jul 2005		**Phase of development:** Phase 3b
Objectives: The objective of this trial was to assess the tolerability of overnight switching from ropinirole, pramipexole, or cabergoline therapy to the rotigotine transdermal system and its effect on symptoms in subjects with idiopathic Parkinson's disease.		
Methodology: This was an open-label, multicenter, multinational trial to assess the tolerability of overnight switching from ropinirole, pramipexole, or cabergoline therapy to the rotigotine transdermal system and its effect on symptoms in subjects with idiopathic Parkinson's disease. All subjects received rotigotine based on the dose of dopamine agonist each subject was taking upon entry into the trial. Each subject was to complete a Pretreatment Period (within 28 days before the overnight switch to rotigotine), a Baseline Visit (Day 0), and a 28-day Treatment Period. Subjects who elected not to continue into the open-label extension (SP833) completed the End of Treatment assessments, entered a De-escalation Period and returned in 30 days for a Safety Follow-Up 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 130 subjects were planned to be enrolled: 50 subjects currently taking ropinirole, 50 subjects currently taking pramipexole, and (in the [redacted] only) 30 subjects currently taking cabergoline in order to obtain 40 subjects each on ropinirole and pramipexole and 20 subjects on cabergoline for evaluation.

One hundred and nineteen subjects were enrolled, and 116 subjects were treated in the trial, with 47 subjects previously taking ropinirole, 47 subjects previously taking pramipexole, and 22 subjects previously taking cabergoline.

Diagnosis and main criteria for inclusion:

Subjects were male or female, aged ≥18 years. Subjects had 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. Subjects were not satisfactorily controlled on a total daily dose of ropinirole up to 9.0mg, pramipexole up to 2.0mg or cabergoline up to 3.0mg. If the subject was receiving levodopa, either short-acting or sustained-release (in combination with benserazide or carbidopa), the total daily dose must have been stable for 28 days prior to the Baseline Visit and must have remained stable for the duration of the trial. If the subject was receiving an anticholinergic agent (eg, benztropine, trihexyphenidyl, parsitan, procyclidine, biperiden), a monoamine oxidase B inhibitor (eg, selegiline), or an N-methyl-d-aspartate-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.

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

Test product: Rotigotine doses included 4.5mg/10cm^2 patch (Batch Number: [redacted]), 9.0mg/20cm^2 (Batch Number: [redacted] 13.5mg/30cm^2 (Batch Number: [redacted] or 18.0mg/40cm^2 (Batch Number: [redacted]

Dosing of rotigotine depended on the dose of dopamine agonist each subject was currently taking. The dose of rotigotine given was based on the below equivalency chart:

Starting dopamine agonist:	**mg/day**	**mg/day**	**mg/day**	**mg/day**
Ropinirole	2.0	4.0	6.0	8.0-9.0
Pramipexole	0.5	1.0	1.5	2.0
Cabergoline	0.8	1.5	2.25	3.0
Were switched to:				
Rotigotine	4.5	9.0	13.5	18.0

Subjects on ropinirole or pramipexole took their last dose at bedtime and then applied rotigotine patch(es) upon awakening the next morning. Subjects on cabergoline applied rotigotine patches 24 hours after the final dose of cabergoline. All subjects applied a patch once daily for 24 hours. 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.

Although the proposed doses were generally equivalent, the clinical effect of switching a subject from one dopamine agonist to another could vary across subjects. It was, therefore, expected that a rotigotine dose adjustment may be required for some subjects. If dose modification was necessary, a subject was required to visit the clinic for an Unscheduled Visit.

Subjects who elected not to enroll in the 2-year open-label extension entered the De-escalation Period. Each de-escalation step was a decrease of 4.5mg/10cm^2 every other day to 0mg; the dose De-escalation Period could last up to 6 days.

Duration of treatment: The maximal duration of trial participation per subject was approximately 13 weeks, including the Pretreatment Period, Treatment Period, De-escalation Period, and 30-day Safety Follow-Up Visit.

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Reference therapy, dose and mode of administration, batch number: All subjects received rotigotine in this trial.

Criteria for evaluation:

Efficacy: Efficacy of rotigotine was assessed by change from Baseline to the End of Treatment in the Unified Parkinson's Disease Rating Scale (UPDRS) Parts I, II, III, and IV scores; severity of illness and global improvement as measured by the Clinical Global Impression (CGI), Patient Global Impression (PGI), and Parkinson's Disease Questionnaire (PDQ-8); and improvements in sleep as measured by the Parkinson's Disease Sleep Scale (PDSS) and Epworth Sleepiness Scale (ESS). Subjects also completed a Patient Treatment Preference Scale. This trial was exploratory and no primary or secondary efficacy endpoints were specified. Efficacy data were analyzed descriptively.

Safety and tolerability: Safety was evaluated by extent of exposure, physical and neurological examinations, clinical laboratory tests, adverse event (AE) assessments, 12-lead electrocardiograms (ECGs), vital signs, and application site assessment. Other measurements included a subject-rated assessment of patch adhesiveness. Safety data were analyzed descriptively.

Although no specific primary or secondary variables were defined for this trial, specific measures were used to assess the tolerability of the switch between each pretreatment group and the rotigotine patch. Specific tolerability endpoints included:

(1) The total number of subjects completing the trial: (a) from Baseline to End of Treatment, (b) on their original treatment assignment from Baseline to End of Treatment, and (c) with at least 1 dose adjustment from Baseline to End of Treatment.

(2) Subjects with dose reductions and occurrence of AEs: (a) drop outs due to AEs with onset during the 5 half-life overlap period for each pretreatment group, (b) drop outs during the 5 half-life overlap period due to AE for each pretreatment group, (c) dose reductions due to AEs with onset during the 5 half-life overlap period for each pretreatment group, (d) dose reductions during the 5 half-life overlap period due to AE for each pretreatment group, and (e) incidence rates of AEs for the period of time between the Pretreatment Visit and the switch to rotigotine, during the switch (5 half-life overlap period), and during treatment after the switch (after 5 half-life overlap period).

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Statistical methods:

Due to the exploratory nature of this trial, there was not a specified primary or secondary variable for analysis. No formal statistical testing was performed on any of the data collected in this trial. Analyses were descriptive in nature only and used all available data for subjects receiving at least 1 dose of trial medication (ie, Safety Set).

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 Institute, Cary, NC, USA) using validated program code according to SCHWARZ BIOSCIENCES' Standard Operating Procedures (SOPs) or authorized Contract Research Organization (CRO) SOPs. All statistical analyses were performed in a descriptive way only. 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 included: n (number of subjects with non-missing values), mean, standard deviation, as well as median, minimum, and maximum. Statistics for categorical variables consisted of listing out the possible categorical outcomes (or collections of categories) and then providing the total counts and percentages of subjects falling within them. Unless otherwise specified, percentages were calculated with a denominator using the number of subjects qualifying for the table or figure within each column group (eg, previous therapy: ropinirole, pramipexole, cabergoline, total).

For coding and consolidating AEs and medical history (past and/or concomitant diseases) into categories of System Organ Class, High Level Term (only for AEs) and Preferred Term, the Medical Dictionary for Regulatory Activities (MedDRA) Version 8.0 was used. Concomitant and previous medications were coded using the World Health Organization (WHO)-Drug Dictionary (WHO-DD, Version 2004 second quarter), and diseases according to the International Classification of Disease, Clinical Modification (MedDRA Version 8.0). AEs were also coded into categories of body system and preferred term and provided in the trial's analysis files, using the WHO-Adverse Reaction Terminology (WHO-ART, Version 1993 with SCHWARZ BIOSCIENCES amendments). However, no presentations or analyses were planned with this coding. After database lock, the clinical database and safety database were upgraded to MedDRA Version 8.1 and reconciliation was performed for consistency. All of the AE data displays are presented using MedDRA Version 8.1.

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Summary and conclusions:

Efficacy:

- Subjects switched from an oral dopamine agonist (pramipexole, ropinirole, or carbergoline) to rotigotine transdermal patch experienced no loss of efficacy.
- Improvements were seen across pretreatment groups in UPDRS Parts I-IV scores. Upon switch to rotigotine, the largest mean improvements for all subjects were seen in UPDRS Part III (motor examination). Improvement was largest for each part of the UPDRS in subjects previously taking cabergoline.
- Improvements in Parkinsonian symptoms were seen in subjects upon switching to rotigotine, as assessed by a variety of standard Parkinson's disease scales. Improvements were observed in the CGI and PGI. There were no substantial changes in the PDSS, ESS, and PDQ-8. Although changes were minimal, the largest improvements were consistently seen in subjects taking cabergoline as prior dopamine agonist therapy.

Safety and tolerability results:

- Switching from an oral dopamine agonist (pramipexole, ropinirole, or carbergoline) to rotigotine transdermal patch was well tolerated.
- Approximately 90% of all subjects completing the trial did not require a dose adjustment.
- Adverse events were consistent with the expected effects of dopamine receptor stimulation and the use of a transdermal delivery system. The AEs were similar among pretreatment groups.
- Subjects reported AEs that were generally mild or moderate in intensity. The most common treatment-emergent AEs (ie, those having an incidence ≥5% in any pretreatment group) included application and instillation site reactions, nausea, somnolence, headaches, insomnia, depression, and nasopharyngitis.
- Two subjects reported 2 treatment-emergent SAEs. A total of 5 subjects reported 6 AEs leading to discontinuation.
- Changes in clinical laboratory values were minimal. No ECG changes were attributable to rotigotine treatment.

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Conclusions:

- Subjects switched from an oral dopamine agonist (pramipexole, ropinirole, or carbergoline) to rotigotine transdermal patch experienced no loss of efficacy and was well tolerated.
- Approximately 90% of all subjects completing the trial did not require a dose adjustment.
- The AEs seen are generally similar to those attributed to other dopamine agonists and transdermal delivery systems.
- Patients preferred the rotigotine transdermal patch over their previous oral dopamine agonist therapy.

Report date: 19 Apr 2006