CT Registry ID#: NCT00242008 (ClinicalTrials.gov Identifier number)
Study No.: SP824

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Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Neupro	Rotigotine	Parkinson's disease

Name of Sponsor/Company: Schwarz Pharma

Title of Study:

A phase 3b, open-label, multicenter, multinational trial to assess the tolerability of switching patients from ropinirole, pramipexole, or cabergoline to the rotigotine transdermal system and its effect on symptoms in patients with idiopathic Parkinson's disease

Investigator(s) (number only):	12
Study Center(s) (number only):	12

Length of Study:	Maximum 13 weeks per patient	**Phase of Development:**	3b
Date first patient enrolled:	21 December 2004		
Date last patient completed:	11 July 2005		

Abstract:

This open-label multicenter trial was designed to assess tolerability and effect on symptoms of overnight switching from oral ropinirole, pramipexole, or cabergoline to rotigotine transdermal patch in patients with established idiopathic Parkinson disease (PD). Male or female patients, aged ≥18 years, with PD (Hoehn & Yahr Stage I-IV), bradykinesia as the cardinal sign, at least one of the following: resting tremor, rigidity, or impaired postural reflexes, and not adequately controlled with daily oral doses of ropinirole up to 9 mg/day, pramipexole (as the salt) up to 2 mg/day, or cabergoline 3 mg/day were included in this trial. Patients receiving levodopa with or without benserazide or carbidopa, an anticholinergic agent, or an N-methyl-d-aspartate antagonist needed to have been on a stable dose of the drug for ≥28 days before baseline visit and for the duration of the trial. Each patient completed a pretreatment period within 28 days preceding baseline visit followed by a 28-day treatment period, and, for those not opting to continue into the open-label long-term extension study (SP833: NCT00505687), a safety follow-up visit 30 days later.

Patients on ropinirole 2 mg/day, pramipexole 0.5 mg/day, or cabergoline 0.8 mg/day were switched to

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2 mg/24h rotigotine transdermal patch. Correspondingly, those on ropinirole 4 mg/day, pramipexole 1 mg/day, or cabergoline 1.5 mg/day were switched to 4 mg/24h rotigotine transdermal patch. Likewise, those on ropinirole 6 mg/day, pramipexole 1.5 mg/day, or cabergoline 2.25 mg/day were switched to 6 mg/24h rotigotine transdermal patch. Similarly, those on ropinirole 8 to 9 mg/day, pramipexole 2 mg/day, or cabergoline 3 mg/day were switched to 8 mg/24h rotigotine transdermal patch.

Tolerability of the switch was evaluated by the number of patients completing the scheduled 28-day treatment period, need for rotigotine dose reductions, and dropouts due to adverse events. Additional safety assessments included adverse events, clinical laboratory tests, 12-lead electrocardiograms, vital signs, and application site assessment. Efficacy assessment relied on changes from baseline to the end of treatment in Unified Parkinson's Disease Rating Scale, PD symptoms, clinical global (CGIC), and patient global (PGIC) impressions of change, and patient's preference of dopaminergic agonist. Due to the exploratory nature of this trial, primary or secondary efficacy endpoints were not specified nor was any formal statistical testing done; all analyses were descriptive in nature.

Publication Reference(s) based on the study:

LeWitt PA, Boroojerdi B, MacMahon D, Patton J, Jankovic J for the SP824 Investigator Group. Overnight switch from oral dopaminergic agonists to transdermal rotigotine patch in patients with Parkinson disease. Clin Neuropharmacol 2007;30(5):256-65.

Number of Patients:	**Total switched to rotigotine**	**Previous oral dopaminergic agonist**		
		Ropinirole	**Pramipexole**	**Cabergoline**
Planned, N:	130	50	50	30
Enrolled, N:119	116	47	47	22
Completed, n (%):	104 (89.7)	43 (91.5)	40 (85.1)	21 (95.5)
Number of Patients Withdrawn, n (%):	12 (10.3)	4 (8.5)	7 (14.9)	1 (4.5)
Due to Adverse Events, n (%):	5 (4.3)	2 (4.3)	3 (6.4)	0
Due to Other Reasons, n (%):	7 (6.0)	2 (4.3)	4 (8.5)	1 (4.5)
Demography:				
Gender (Females/Males):	39/77	12/35	18/29	9/13
Age (years), mean(SD):	62.8 ± 9.9	61.2 ± 10.3	61.6 ± 9.4	68.8 ± 9.9
Duration of PD (Mean ± SD), years:	5.0 ± 4.4	4.9 ± 4.0	4.6 ± 4.7	6.2 ± 4.7
Patients on concomitant levodopa, n(%)	73 (62.9)	30 (63.8)	25 (53.2)	18 (81.8)

Safety Outcomes: *(Summary of treatment emergent adverse events, deaths, other serious adverse events and certain other significant adverse events)*

Fifty-one patients (44%) reported an adverse event after the switch to rotigotine transdermal patch. Five patients (5/116 = 4.3%) discontinued during the trial due to adverse events. One patient each

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discontinued due to tachycardia, nausea, depression, insomnia, and contact dermatitis. Two of the patients had previously taken ropinirole and 3 pramipexole. Dose adjustments made for 15 patients (12.9%) included 12 increases (2 for prior ropinirole, 6 for prior pramipexole, and 4 for prior cabergoline), and 3 decrements (1 from each of the previous dopamine agonist therapy groups). These 3 patients needed dose reduction due to the onset of adverse events during the 5 half-life overlap period when switching from their previous dopamine agonist to rotigotine transdermal patch. Two of the patients needing dose reduction were on 4 mg/24h rotigotine and 1 on 8 mg/24h. Of patients requiring rotigotine dose adjustment, 11 completed the entire treatment period, whereas 4 patients prematurely discontinued the trial. Serious treatment-emergent adverse events were reported by 2 patients, in one of whom a possible causal relation to rotigotine transdermal patch was suggested by investigator because of contact dermatitis at site of patch application. There were no clinically relevant changes in vital signs, laboratory parameters, neurological or physical signs. A 72-year old male patient who had baseline premature ventricular contractions and was receiving beta-blocker therapy for hypertension developed atrial fibrillation on Day 28 and was considered unrelated to trial drug. There were no QT_c increases of 60 ms or greater. The mean maximal change from baseline recorded in QT_cB during the treatment period was 1.4 msec.

Treatment Emergent AEs: if applicable	**Total switched to rotigotine N = 116**	**Previous oral dopaminergic agonist**		
		Ropinirole N = 47	**Pramipexole N = 47**	**Cabergoline N = 22**
Patients with at least 1 TEAE, n (%)	51 (44.0)	18 (38.3)	22 (46.8)	11 (50.0)
Patients with TEAEs (*by Primary System Organ Class*)	n (%) [n considered drug-related by the Investigator]			
Gastrointestinal disorders	12 (10.3) [9]	4 (8.5) [3]	6 (12.8) [4]	2 (9.1) [2]
Nausea	7 (6.0) [7]	2 (4.3) [2]	4 (8.5) [4]	1 (4.5) [1]
General disorders and administration site conditions	13 (11.2) [13]	5 (10.6) [5]	4 (8.5) [4]	4 (18.2) [4]
Application site erythema	4 (3.4) [4]	2 (4.3) [2]	0	2 (9.1) [2]
Application site irritation	1 (0.9) [1]	0	1 (2.1) [1]	0
Application site pruritus	5 (4.3) [5]	3 (6.4) [3]	1 (2.1) [1]	1 (4.5) [1]
Fatigue	3 (2.6) [2]	1 (2.1) [0]	2 (4.3) [2]	0
Infections and infestations	5 (4.3) [0]	0	5 (10.6) [0]	0
Nasopharyngitis	3 (2.6) [0]	0	3 (6.4) [0]	0
Nervous system disorders	19 (16.4) [14]	5 (10.6) [3]	11 (23.4) [9]	3 (13.6) [2]
Somnolence	7 (6.0) [7]	2 (4.3) [2]	3 (6.4) [3]	2 (9.1) [2]
Headache	6 (5.2) [4]	1 (2.1) [0]	5 (10.6) [4]	0

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Psychiatric disorders	12 (10.3) [8]	6 (12.8) [5]	5 (10.6) [3]	1 (4.5) [0]
Depression	4 (3.4) [0]	3 (6.4) [0]	1 (2.1) [0]	0
Insomnia	5 (4.3) [4]	3 (6.4) [3]	2 (4.3) [1]	0
Cardiac disorders	3 (2.6) [1]	3 (6.4) [1]	0	0
Infections and infestations	4 (3.4) [0]	0	4 (8.5) [0]	0
Injury, poisoning, and procedural complications	3 (2.6) [0]	1 (2.1) [0]	1 (2.1) [0]	1 (4.5) [0]
Metabolism and nutrition disorders	2 (1.7) [1]	0	1 (2.1) [1]	1 (4.5) [0]
Musculoskeletal and connective tissue disorders	8 (6.9) [3]	3 (6.4) [0]	3 (6.4) [1]	2 (9.1) [2]
Respiratory, thoracic, and mediastinal disorders	4 (3.4) [0]	1 (2.1) [0]	2 (4.3) [0]	1 (4.5) [0]
Skin and subcutaneous tissue disorders	5 (4.3) [3]	1 (2.1) [1]	3 (6.4) [1]	1 (4.5) [1]
Death, SAEs, and other SAEs, if applicable				
Death, n (%):	0	0	0	0
Patients with Treatment-Emergent SAEs, n (%):	2 (1.7)	1 (2.1)	0	1 (4.5)
Patients with Treatment-Emergent SAEs (by Primary System Organ Class)	n (%) [n considered drug-related by the Investigator]			
Dermatitis, contact	1 (0.9) [1]	1 (2.1) [1]	0	0
Wrist fracture	1 (0.9) [0]	0	0	1 (4.5) [0]

Primary & Secondary Outcomes:

This exploratory trial did not specify any primary or secondary outcomes.

Patients switching from the oral dopaminergic agonists to rotigotine experienced improvements in PD signs and symptoms. As compared with baseline UPDRS scores, rotigotine treatment resulted in improvement in UPDRS Activities of Daily Living (Part II) by 10% and Motor Examination scores (Part III) by 9.6%. CGIC scores indicated global improvement in 69 (59.5%) patients after switch to rotigotine transdermal patch; 71 (61.2%) patients by PGIC score indicated improvement over their previous oral dopamine agonist therapy. Overall, 89 patients (76.7%) preferred rotigotine transdermal patch to their previous oral dopaminergic agonist.

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