CT Registry ID#: NCT00244387 (ClinicalTrials.gov Identifier number)

Study No.: SP515

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Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Neupro®	Rotigotine	Advanced-stage, Parkinson's disease

Name of Sponsor/Company: SCHWARZ BIOSCIENCES, Inc. A member of the UCB group

Title of Study:

A multi-center, multinational, phase III, randomized, double-blind, double-dummy, 3-arm parallel group, placebo- and pramipexole-controlled trial of the efficacy and safety of rotigotine patch in subjects with advanced-stage, idiopathic Parkinson's disease who are not well controlled on levodopa

Investigator(s) (number only): 89

Study Center(s) (number only): 77

Length of Study: Maximum 32 weeks per patient
Date first patient enrolled: 02 Mar 2004
Date last patient completed: 12 Jul 2005

Phase of Development: 3

Abstract:

SP515 was a Phase 3, multi-center, multi-national, randomized, double-blind, placebo-controlled, 3-arm parallel group trial of rotigotine in subjects with advanced-stage, idiopathic Parkinson's disease who were not well-controlled on levodopa (L-DOPA). The primary objective of this trial was to show that rotigotine is efficacious as an adjuvant therapy in subjects with advanced-stage Parkinson's disease. Secondary objectives included assessment of the tolerability and safety of rotigotine. Subjects were included if they were ≥30 years of age with idiopathic Parkinson's disease of >3 years duration (with cardinal sign of bradykinesia, plus the presence of ≥1 of the following: resting tremor, rigidity, or impairment of postural reflexes) and without any known or suspected cause of Parkinsonism. Subjects were required to have Hoehn & Yahr stage II through IV in both the "on" and "off" states and have a Mini-Mental State Examination score of ≥25. All subjects were not adequately controlled on L-DOPA, but were on a stable dose of L-DOPA of ≥300mg/day in combination with benserazide or carbidopa for ≥28 days prior to Baseline. Those subjects receiving an anticholinergic agent, a monoamine oxidase B (MAO-B) inhibitor, or an N-methyl-D-aspartate (NMDA) antagonist, were on a stable dose for ≥28 days prior to Baseline and were maintained on that dose for the duration of the trial. Subjects were on stable doses of all anti-Parkinsonian medications for ≥20 days prior to completing 6 Pretreatment diaries.

Subjects were titrated to an optimal dose of up to rotigotine 36mg/day (16mg/24h) or pramipexole 4.5mg/day. The trial consisted of a 4-week Pretreatment Phase, a Dose Titration Phase (up to 7 weeks), a 16-week Maintenance Phase, a De-escalation Phase (up to 6 days), and a Safety-Follow-Up Phase (~4 weeks).

For the United States (US), efficacy was determined by the reduction in absolute time spent "off" from

CT Registry ID#: NCT00244387 (ClinicalTrials.gov Identifier number)

Study No.: SP515

Baseline to the end of the double-blind Maintenance Phase. For the European Union (EU), efficacy was determined by the subject's response to therapy. A "responder" was a subject with ≥30% decrease in absolute time spent "off" from Baseline to the end of the double-blind Maintenance Phase. Secondary efficacy variables for both the US and EU included the following: change and percent change from Baseline to the end of the Maintenance Phase in absolute and relative time spent "on"; change from Baseline to the end of the Maintenance Phase in the number of "off" periods; change from Baseline to the end of the Maintenance Phase in the status of the subject (on/off) after wake-up; change from Baseline to the end of the Maintenance Phase in Unified Parkinson's Disease Rating Scale (UPDRS) Parts II, III, and IV during "on" periods; and area under the curve over the Maintenance Phase for the absolute time spent "off" during the Maintenance Phase of the trial.

Pharmacokinetics: The plasma concentrations of rotigotine were measured in approximately 60 subjects.

Number of Patients:	**Placebo**	**Rotigotine**	**Pramipexole**	**Total**
Planned, N:	90	180	180	450
Enrolled (and randomized), N:	101	204	201	506
Completed, n (%):	75 (74.3)	181 (88.7)	171 (85.1)	427 (84.4)
Number of Patients Withdrawn, n (%):	26 (25.7)	23 (11.3)	30 (14.9)	79 (15.6)
Due to Adverse Events, n (%):	6 (5.9)	11 (5.4)	14 (7.0)	31 (6.1)
Due to Other Reasons, n (%):	20 (19.8)	12 (5.9)	16 (8.0)	48 (9.5)
Demography:				
Gender (Females/Males):	29/70	72/133	88/114	189/317
Age (years), mean (SD):	64.7 ± 10.06	64.3 ± 8.94	63.3 ± 9.72	64.0 ± 9.48
Race, n (%)				
White	97 (98.0)	200 (97.6)	195 (96.5)	492 (97.2)
Black	0	0	1 (0.5)	1 (0.2)
Asian	0	1 (0.5)	1 (0.5)	2 (0.4)
Other	2 (2.0)	4 (2.0)	5 (2.5)	11 (2.2)
Duration of PD (Mean ± SD), years:	8.3 ± 4.9	8.8 ± 4.4	8.4 ± 4.7	8.6 ± 4.63

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

The incidences of adverse events (AE) were generally similar among the treatment groups and were generally of mild or moderate intensity. The most common treatment-emergent AEs that occurred more frequently in rotigotine-treated subjects compared to placebo- and pramipexole-treated subjects were application and instillation site reactions (20.5% in the rotigotine group vs 8.4% in the pramipexole and 10.1% in the placebo group), followed by nausea (17.1% in the rotigotine group vs 12.9% in the pramipexole and 11.1% in the placebo group), and somnolence (12.2% in the rotigotine group vs 11.9% in the pramipexole and 8.1% in the placebo group). The only AEs clearly related to the rotigotine patch and not typical of other dopamine agonists were application and instillation site reactions, which predominantly included erythema and pruritus. Most application and instillation site reactions in all treatment groups were mild or moderate in intensity, and most resolved by the end of treatment without requiring a dose adjustment. No rotigotine-treated subjects reported sleep attacks.

Two deaths were reported during this trial. One subject receiving placebo died of hepatic failure. This fatal AE was judged by the investigator to be not related to trial medication. One subject receiving rotigotine

died as a result of a road traffic accident. This fatal AE was judged by the investigator to be unlikely related to trial medication. The incidence of AEs leading to discontinuation (5.1% placebo, 5.4% rotigotine, 7.4% pramipexole) and the incidence of SAEs was similar among treatment groups with no obvious trends. There were no clinically relevant changes in vital signs, laboratory parameters (including ECG), or physical examination.

Treatment Emergent AEs (Safety Population as Treated) :	Placebo (N=99)	Rotigotine (N=205)	Pramipexole (N=202)
Incidence of AEs occurring in ≥5% in any treatment group, n (%) (by Primary System Organ Class/Preferred Term)			
Any system organ class	65 (65.7)	141 (68.8)	140 (69.3)
Gastrointestinal disorders	20 (20.2)	58 (28.3)	47 (23.3)
Nausea	11 (11.1)	35 (17.1)	26 (12.9)
General disorders and administration site conditions	20 (20.2)	55 (26.8)	30 (14.9)
Application and instillation site reactions[a]	10 (10.1)	42 (20.5)	17 (8.4)
Application site erythema	5 (5.1)	18 (8.8)	8 (4.0)
Application site pruritus	4 (4.0)	18 (8.8)	5 (2.5)
Musculoskeletal and connective tissue disorders	11 (11.1)	33 (16.1)	27 (13.4)
Back pain	4 (4.0)	12 (5.9)	16 (7.9)
Nervous system disorders	30 (30.3)	83 (40.5)	83 (41.1)
Somnolence	8 (8.1)	25 (12.2)	24 (11.9)
Dyskinesia	3 (3.0)	24 (11.7)	30 (14.9)
Dizziness	4 (4.0)	12 (5.9)	20 (9.9)
Headache	5 (5.1)	7 (3.4)	13 (6.4)
Parkinson's disease[b]	5 (5.1)	5 (2.4)	6 (3.0)
Psychiatric disorders	11 (11.1)	30 (14.6)	42 (20.8)
Perception disturbances[a]	1 (1.0)	10 (4.9)	14 (6.9)
Vascular disorders	11 (11.1)	20 (9.8)	23 (11.4)
Orthostatic hypotension	5 (5.1)	7 (3.4)	9 (4.5)

a. This is a MedDRA high-level term.
b. This preferred term was reported as an AE to indicate a worsening of symptoms

Drug-related TEAEs (as assessed by the Investigator):	Placebo (N=99)	Rotigotine (N=205)	Pramipexole (N=202)
Incidence of drug-related TEAEs occurring in ≥5% in any treatment group, n (%) (by Primary System Organ Class/Preferred Term)			
Any system organ class	38 (38.4)	113 (55.1)	106 (52.5)
Gastrointestinal disorders	13 (13.1)	46 (22.4)	38 (18.8)
Nausea	10 (10.1)	34 (16.6)	25 (12.4)
General disorders and administration site conditions	10 (10.1)	46 (22.4)	23 (11.4)

CT Registry ID#: NCT00244387 (ClinicalTrials.gov Identifier number)

Study No.: SP515

Application and instillation site reactions[a]	7 (7.1)	42 (20.5)	16 (7.9)
Application site erythema	3 (3.0)	17 (8.3)	7 (3.5)
Application site pruritus	2 (2.0)	18 (8.8)	4 (2.0)
Nervous system disorders	20 (20.2)	63 (30.7)	68 (33.7)
Dyskinesia	3 (3.0)	24 (11.7)	30 (14.9)
Somnolence	7 (7.1)	17 (8.3)	22 (10.9)
Dizziness	3 (3.0)	9 (4.4)	16 (7.9)
Psychiatric disorders	7 (7.1)	24 (11.7)	34 (16.8)
Perception disturbances[a]	1 (1.0)	10 (4.9)	14 (6.9)
Vascular disorders	8 (8.1)	9 (4.4)	14 (6.9)
Orthostatic hypotension	5 (5.1)	6 (2.9)	9 (4.5)

a. This is a MedDRA high-level term

Death, SAEs, and other SAEs, if applicable	**Placebo (N=99)**	**Rotigotine (N=205)**	**Pramipexole (N=202)**
Death, n (%):	1 (1.01)	1 (0.49)	0
Patients with Treatment-Emergent SAEs, n (%):	9 (9.1)	19 (9.3)	15 (7.4)
Treatment-Emergent SAEs occurring in >1 patient in any treatment group, n (%) (by Primary System Organ Class/Preferred Term)	n (%) [n considered drug-related by the Investigator]		
Cardiac disorders	1 (1.0) [1]	3 (1.5) [2]	0
Gastrointestinal disorders	2 (2.0) [0]	4 (2.0) [1]	3 (1.5) [0]
General disorders and administration site conditions	0	2 (1.0) [2]	1 (0.5) [1]
Application site dermatitis	0	2 (1.0) [2]	0
Injury, poisoning and procedural complications	0	2 (1.0) [0]	0
Nervous system disorders	2 (2.0) [0]	3 (1.5) [2]	1 (0.5) [1]
Psychiatric disorders	1 (1.0) [0]	0	3 (1.5) [4]
Surgical and medical procedures	0	2 (1.0) [0]	1 (0.5) [0]

Primary & Secondary Efficacy Outcomes:

Rotigotine decreased the absolute "off" time at the end of the Maintenance Phase by 2.46 hours compared with a decrease of 0.88 hours in placebo-treated subjects ($p<0.001$) and a decrease of 2.81 hours in pramipexole-treated subjects. Statistical analysis showed noninferiority of rotigotine versus pramipexole using a noninferiority margin of 1.2 hours. Rotigotine and pramipexole treatment both resulted in a higher proportion of subjects who had a ≥30% decrease in the absolute amount of "off" time at the end of Maintenance (59.7% and 67.0%, respectively) compared with placebo (35.0%). The proportion of responders receiving rotigotine was statistically significantly different from the placebo group ($p<0.001$). For rotigotine and pramipexole, noninferiority could not be shown in the Full Analysis Set (FAS) using a noninferiority margin of -15%. However, in the completer analysis, noninferiority could be demonstrated ($p=0.047$). Results for the Per Protocol Set were similar to the FAS. The secondary endpoints were supportive of the primary efficacy endpoint and showed consistent improvement in the rotigotine group.

CT Registry ID#: NCT00244387 (ClinicalTrials.gov Identifier number) **Study No.: SP515**	
Pharmacokinetics: The mean rotigotine plasma concentrations measured in subjects with advanced-stage Parkinson's disease increased in a dose-proportional manner during the Titration Phase and remained generally stable throughout the 4-month Maintenance Phase.	
Publication(s):	Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, Rupp M, Boroojerdi B; SP 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol. 2007 Jun;6(6):513-20.
Date of report:	08 May 2006