Approved by UCB 30-Jul-2008

Clinical Study Summary (CSS)

CT Registry ID#: *NCT00136045 (ClinicalTrials.gov Identifier number)*
Study No.: SP790

These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
Neupro® transdermal patch	Rotigotine	Restless legs syndrome

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

Title of Study:
A multi-center, randomized, double-blind, placebo-controlled, four-arm parallel-group trial to investigate the efficacy and safety of three different transdermal doses of rotigotine in subjects with idiopathic restless legs syndrome

Investigator(s) (number only): 50

Study Center(s) (number only): 49

Length of Study:	8 month maximum	Phase of Development:	3
Date first patient enrolled:	31-May-2005		
Date last patient completed:	23-Aug-2006		

Abstract:
SP790 was a Phase 3, multicenter, multinational, randomized, double-blind, placebo-controlled, 4-arm, parallel-group trial of rotigotine in subjects with restless legs syndrome (RLS). The primary efficacy outcome was assessed by the absolute change from Baseline at the end of the Maintenance Period in the International Restless Legs Scale (IRLS) sum score and the Clinical Global Impressions (CGI) Item 1 (severity of illness) score. The following safety variables were measured: adverse events (AEs) reported spontaneously by the subject or observed by the investigator, changes in laboratory tests (hematology and blood chemistry), changes in vital signs (including orthostatic assessment), physical and neurological examination findings, changes in 12-lead electrocardiograms (ECGs), subject's rating of daytime sleepiness as measured by the Epworth Sleepiness Scale, changes in menstrual and sexual function, change from Baseline in the Augmentation Severity Rating Scale (ASRS) at the end of the Maintenance Period, changes in Medical Outcomes Study Sleep Scale score from Baseline at the end of the Maintenance Period, changes in the Self-Rating Depression Scale, Global Subject Rating of Tolerability, CGI Item 4, application site assessment, and patch adhesiveness.

Subjects were included if they were ≥18 and ≤75 years of age; met the diagnosis of idiopathic RLS based on the cardinal clinical features according to the International Restless Legs Syndrome Study Group; had an initial response to previous dopaminergic treatment for RLS or had no previous dopaminergic treatment (ie, de novo); had a score of ≥15 on the IRLS (indicating moderate to severe RLS) at Baseline; and scored ≥4 points on the CGI Item 1 assessment (indicating at least moderately ill) at Baseline. Subjects were excluded from the trial if they had secondary RLS; a history of sleep disturbances; other central nervous diseases (eg, Parkinson's disease); were pregnant; had a QTc interval of ≥500ms at Visit 1, or had an average QTc interval of ≥500ms at Baseline; had symptomatic orthostatic hypotension.

Subjects were enrolled and randomized to receive placebo, 1, 2, or 3mg/24h rotigotine. All subjects began the 3-week Titration Period at a daily dosage of 1mg rotigotine/placebo. Subjects were up-titrated weekly in 1mg/24h increments to their assigned daily dose. After the Titration Period was completed, subjects entered the 6-month Maintenance Period. A 7-day Taper Period was provided to allow for safe, gradual withdrawal from trial medication. Subjects who completed the 6-month Maintenance Period and 7-day Taper Period were eligible to participate in an open-label extension trial. Subjects who did not complete the 6-month Maintenance

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Period or who chose not to participate in the open-label extension trial completed a 30-day Safety Follow-Up Period.

Number of Patients:	**Placebo**	**Rotigotine 1mg/24h**	**Rotigotine 2mg/24h**	**Rotigotine 3mg/24h**	**All Subjects**
Planned for enrollment, N:	100	100	100	100	450[a]
Randomized, N:	117	115	112	114	458
Completed, n (%):	68 (58.1)	84 (73.0)	87 (77.7)	74 (64.9)	313 (68.3)
Number of Patients Withdrawn, n (%):	49 (41.9)	31 (27.0)	25 (22.3)	40 (35.1)	145 (31.7)
Withdrawn due to Adverse Events, n (%):	4 (3.4)	14 (12.2)	14 (12.5)	24 (21.1)	56 (12.2)
Withdrawn for Other Reasons, n (%):	45 (38.5)	17 (14.8)	11 (9.8)	16 (14.0)	89 (19.4)
Demography:					
Gender (Females/Males):	81/36	84/31	85/27	83/31	333/125
Age (years), mean (SD):	59.8 (10.0)	57.2 (10.4)	57.2 (12.3)	56.3 (12.0)	57.6 (11.3)
Race, n (%):					
White	117 (100)	115 (100)	112 (100)	113 (99.1)	457 (99.8)
Asian	0	0	0	1 (0.9)	1 (0.2)

a. 450 subjects planned for enrollment to obtain 400 randomized subjects

Safety Outcomes:

- Summary of treatment emergent adverse events, deaths, other serious adverse events and certain other significant adverse events:

Rotigotine was well tolerated in this trial. Most adverse events (AEs) were consistent with stimulation of dopamine receptors and use of a transdermal patch. The most frequently occurring AEs were application site reactions, nausea, fatigue, and headache. Application site reactions occurred in 42% of rotigotine-treated subjects; 89% of those subjects had only reactions which were mild or moderate in severity. The incidence of serious adverse events was similar across all rotigotine treatment groups, but higher than the placebo group. Adverse events leading to discontinuation of trial medication occurred in 16% of rotigotine-treated subjects compared to 7% of placebo-treated subjects. The majority of AEs in rotigotine-treated subjects that led to discontinuation from the trial occurred during the Maintenance Period. Overall, there was no evidence for an association between rotigotine treatment and ECG abnormalities or changes at doses up to 3mg/24h. No clinically relevant changes in vital signs (including orthostatic assessment), clinical chemistry, hematology, endocrine parameters, or urinalysis, physical or neurological examination, or menstrual or sexual function were observed. There was no evidence of augmentation based on the results of the ASRS.

Treatment Emergent AEs (TEAEs):	**Placebo (N=117)**	**Rotigotine 1mg/24h (N=115)**	**Rotigotine 2mg/24h (N=112)**	**Rotigotine 3mg/24h (N=114)**	**Rotigotine Total (N=341)**
Patients with ≥5% TEAEs, n (%):*(by Preferred term)*					
Any system organ class	64 (54.7)	84 (73.0)	90 (80.4)	91 (79.8)	265 (77.7)
Headache	11 (9.4)	16 (13.9)	18 (16.1)	20 (17.5)	54 (15.8)
Nausea	6 (5.1)	10 (8.7)	24 (21.4)	22 (19.3)	56 (16.4)
Fatigue	11 (9.4)	9 (7.8)	19 (17.0)	14 (12.3)	42 (12.3)
Nasopharyngitis	8 (6.8)	12 (10.4)	7 (6.3)	8 (7.0)	27 (7.9)
Dizziness	3 (2.6)	5 (4.3)	10 (8.9)	5 (4.4)	20 (5.9)
Hyperhidrosis	4 (3.4)	6 (5.2)	7 (6.3)	5 (4.4)	18 (5.3)
Dry mouth	4 (3.4)	4 (3.5)	6 (5.4)	8 (7.0)	18 (5.3)
Pruritus	3 (2.6)	7 (6.1)	2 (1.8)	5 (4.4)	14 (4.1)

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Vertigo	2 (1.7)	7 (6.1)	6 (5.4)	2 (1.8)	15 (4.4)
Insomnia	4 (3.4)	2 (1.7)	2 (1.8)	9 (7.9)	13 (3.8)
Sleep disorder	2 (1.7)	2 (1.7)	6 (5.4)	6 (5.3)	14 (4.1)
Back pain	6 (5.1)	3 (2.6)	2 (1.8)	4 (3.5)	9 (2.6)
Drug-related TEAEs (as determined by the investigator):	**Placebo (N=117)**	**Rotigotine 1mg/24h (N=115)**	**Rotigotine 2mg/24h (N=112)**	**Rotigotine 3mg/24h (N=114)**	**Rotigotine Total (N=341)**
Patients with ≥5% drug-related TEAEs, n (%):*(by Preferred term)*					
Any system organ class	38 (32.5)	69 (60.0)	79 (70.5)	84 (73.7)	232 (68.0)
Application and instillation site reactions[a]	2 (1.7)	40 (34.8)	46 (41.1)	59 (51.8)	145 (42.5)
Nausea	4 (3.4)	10 (8.7)	24 (21.4)	21 (18.4)	55 (16.1)
Headache	8 (6.8)	11 (9.6)	14 (12.5)	18 (15.8)	43 (12.6)
Fatigue	11 (9.4)	8 (7.0)	17 (15.2)	12 (10.5)	37 (10.9)
Dizziness	3 (2.6)	5 (4.3)	8 (7.1)	5 (4.4)	18 (5.3)
Dry mouth	4 (3.4)	3 (2.6)	6 (5.4)	8 (7.0)	17 (5.0)
Hyperhidrosis	3 (2.6)	6 (5.2)	7 (6.3)	5 (4.4)	18 (5.3)
Insomnia	4 (3.4)	0	0	8 (7.0)	8 (2.3)
Vomiting	1 (0.9)	6 (5.2)	5 (4.5)	1 (0.9)	9 (2.6)
a. MedDRA high level term					
Death, SAEs, and Other SAEs :	**Placebo (N=117)**	**Rotigotine 1mg/24h (N=115)**	**Rotigotine 2mg/24h (N=112)**	**Rotigotine 3mg/24h (N=114)**	**Rotigotine Total (N=341)**
Death, n (%):	0	0	0	0	0
Patients with SAEs, n (%):(by System Organ Class)	*n (%) [events considered drug-related by the Investigator]*				
Any system organ class	5 (4.3) [0]	7 (6.1) [4]	5 (4.5) [3]	13 (11.4) [5]	25 (7.3) [12]
Cardiac disorders	0	0	0	1 (0.9) [0]	1 (0.3) [0]
Ear and labyrinth disorders	0	1 (0.9) [1]	0	1 (0.9) [0]	2 (0.6) [1]
Gastrointestinal disorders	0	1 (0.9) [0]	0	1 (0.9) [0]	2 (0.6) [0]
General disorders and administration site conditions	0	1 (0.9) [1]	2 (1.8) [2]	4 (3.5) [4]	7 (2.1) [7]
Hepatobiliary disorders	0	0	1 (0.9) [0]	1 (0.9) [0]	2 (0.6) [0]
Infections and infestations	2 (1.7) [0]	0	0	0	0
Injury, poisoning and procedural complications	0	1 (0.9) [0]	1 (0.9) [0]	0	2 (0.6) [0]
Investigations	0	1 (0.9) [2]	0	1 (0.9) [1]	2 (0.6) [3]
Neoplasms benign, malignant and unspecified	1 (0.9) [0]	0	0	3 (2.6) [0]	3 (0.9) [0]
Nervous system disorders	0	0	0	1 (0.9) [0]	1 (0.3) [0]
Reproductive system and breast disorders	1 (0.9) [0]	1 (0.9) [0]	0	0	1 (0.3) [0]

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Surgical and medical procedures	0	1 (0.9) [0]	0	1 (0.9) [0]	2 (0.6) [0]
Vascular disorders	1 (0.9) [0]	0	1 (0.9) [1]	0	1 (0.3) [1]
Primary & Secondary Outcomes: Rotigotine is an effective treatment for RLS as monotherapy at doses ranging from 1 to 3mg/24h. Superiority over placebo at doses ranging from 1 to 3mg/24h was demonstrated for the coprimary variables (mean change from Baseline inIRLS sum score and CGI Item 1 at the end of the Maintenance Period). The dose-dependent decreases (improvements) in the IRLS score and CGI Item 1 were clinically relevant and statistically significant.					
Publication Reference(s) based on the study: Trenkwalder C, Benes H, Poewe W, Oertel WH, Garcia-Borreguero D, de Weerd AW, et al. Efficacy of rotigotine for treatment of moderate-to-severe restless legs syndrome: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2008 Jul;7(7):595-604.					
Date of report: 07-Aug-2007					