Clinical Study Summary (CSS)

CT Registry ID#: *NCT00135993*
Study No.: SP792

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

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

Title of Study:
A multicenter, randomized, double-blind, placebo-controlled, 5-arm parallel-group trial to investigate the efficacy and safety of 4 different transdermal doses of rotigotine in subjects with idiopathic Restless Legs Syndrome

Investigator(s) (number only): 66

Study Center(s) (number only): 60 sites were initiated and 58 sites enrolled at least 1 subject

Length of Study:	~8 months	Phase of Development: 3
Date first subject enrolled:	10 May 2005	
Date last subject completed:	06 Nov 2006	

Abstract:
This was a randomized, double-blind, placebo-controlled, five-arm, parallel-group trial to investigate the efficacy and safety of 4 different transdermal doses of rotigotine in subjects with idiopathic Restless Legs Syndrome (RLS). Subjects were eligible if they were between 18 and 75 years of age and met the diagnosis of idiopathic RLS based on the essential criteria according to the International Restless Legs Syndrome Study Group. In addition, eligible subjects must have had the following: An initial response to previous dopaminergic treatment for RLS or had no previous dopaminergic treatment (ie, de novo), a score of ≥15 on the IRLS (indicating moderate to severe RLS) at Baseline, and a score of ≥4 points on the Clinical Global Impressions (CGI) Item 1 assessment (indicating at least moderately ill) at Baseline.

The primary efficacy outcome was assessed by the absolute change from Baseline at the end of the Maintenance Period in the IRLS sum score and the CGI Item 1 (severity of illness) score. The following secondary efficacy variables were measured: IRLS responder (defined as a subject with a decrease of ≥50% in IRLS sum score from Baseline at the end of the Maintenance Period), CGI Item 1 responder (defined as a subject with a decrease of ≥50% in CGI Item 1 at the end of the Maintenance Period), changes in CGI Items 2 and 3 (continuous) during the Maintenance Period, and change from Baseline in Restless Legs Syndrome-6 Rating Scales (RLS-6) at the end of the Maintenance Period.

Safety was assessed by the following: adverse events (AEs), changes in clinical laboratory parameters, changes in vital signs (including orthostatic assessment), changes in 12-lead ECG data, physical and neurological examination findings, subject's rating of daytime sleepiness using the Epworth Sleepiness Scale, changes in menstrual and sexual function, change from Baseline in the Augmentation Severity Rating Scale 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.

Rotigotine nominal doses included were 0.5mg, 1mg, 2mg, and 3mg/24h. Trial periods consisted of a Run-In Period (Wash-Out Period) of 1 week, a Titration Period of 4 weeks, a 6-month Maintenance Period, a Taper Period of 7 days, and a 30-day Safety Follow-Up Period. Overall, the mean duration of exposure to trial

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medication was 174 days for subjects in the placebo group and 161 days for subjects in the rotigotine treatment groups. Subjects who completed the Maintenance Period and the Taper Period were offered the opportunity to enroll in an open-label extension trial.

Number of Subjects:	**Placebo**	**Rotigotine (mg/24h)**				**All Subjects**
		0.5	**1**	**2**	**3**	
Planned, N:	100	100	100	100	100	500
Randomized, N:	100	99	101	99	106	505
Completed, n (%):	67 (67.0)	76 (76.8)	54 (53.5)	63 (63.6)	60 (56.6)	320 (63.4)
Number of Subjects Withdrawn, n (%):	33 (33.0)	23 (23.2)	47 (46.5)	36 (36.4)	46 (43.4)	185 (36.6)
Withdrawn due to Adverse Events, n (%):	4 (4.0)	16 (13.3)	18 (17.6)	22 (24.2)	26 (28.6)	78 (15.4)
Withdrawn for Other Reasons, n (%):	29 (29.0)	7 (7.1)	29 (28.7)	14 (14.1)	20 (18.9)	107 (21.2)
Demography:	**Placebo**	**Rotigotine (mg/24h)**				**All Subjects**
		0.5	**1**	**2**	**3**	
Gender (Females/Males):	57/43	61/38	57/43	64/35	67/39	306/198
Age (years), mean(SD):	52.7 (12.5)	52.9 (12.8)	51.6 (13.0)	52.8 (12.2)	51.3 (12.3)	52.3 (12.6)
Race, n(%):						
white	92 (92.0)	94 (94.9)	97 (97.0)	93 (93.9)	96 (90.6)	472 (93.7)
black	2 (2.0)	1 (1.0)	2 (2.0)	2 (2.0)	3 (2.8)	10 (2.0)
Asian	0	1 (1.0)	0	0	1 (0.9)	2 (0.4)
Other	6 (6.0)	3 (3.0)	1 (1.0)	4 (4.0)	6 (5.7)	20 (4.0)

Safety Outcomes:
Rotigotine was well tolerated in this trial. Overall, 84% of subjects in the placebo group and 88% of subjects in a rotigotine treatment group reported 1 or more AEs during the Treatment Period. Most AEs were consistent with dopaminergic stimulation and the use of a transdermal patch. The most frequently occurring treatment-emergent AEs were application site reactions, nausea, headache, somnolence, upper respiratory tract infection, and fatigue. Application site reaction was the only AE that seemed to be dose related. Application site reactions occurred in 27% of rotigotine-treated subjects; 95% of those were mild or moderate in intensity. Serious adverse events were reported by the same proportion of rotigotine- and placebo-treated subjects (4%). No trends were evident. Adverse events leading to discontinuation occurred in 20% of rotigotine-treated subjects compared to 4% of placebo-treated subjects. Overall, there was no evidence for an association between rotigotine treatment and ECG abnormalities or changes, including QTc prolongation at doses up to 3mg/24h. No clinically relevant changes in vital signs (including orthostatic assessment), clinical chemistry, hematology, or urinalysis parameters, physical or neurological examination, or menstrual or sexual function were observed at doses up to 3mg/24h.

A summary of AEs is provided below:

Treatment Emergent AEs (TEAEs):	**Placebo**	**Rotigotine (mg/24h)**				**Total Rotigotine (N=404)**
	(N=100)	**0.5 (N=99)**	**1 (N=100)**	**2 (N=99)**	**3 (N=106)**	
Subjects with ≥5% TEAEs, n (%): *(by Preferred term)*						
Any system organ class	84 (84.0)	84 (84.8)	88 (88.0)	89 (89.9)	94 (88.7)	355 (87.9)
Application and instillation site reactions[a]	6 (6.0)	23 (23.2)	17 (17.0)	34 (34.3)	36 (34.0)	110 (27.2)
Nausea	15 (15.0)	18 (18.2)	22 (22.0)	24 (24.2)	23 (21.7)	87 (21.5)
Headache	13 (13.0)	21 (21.2)	17 (17.0)	19 (19.2)	14 (13.2)	71 (17.6)
Somnolence	8 (8.0)	8 (8.1)	10 (10.0)	16 (16.2)	17 (16.0)	51 (12.6)
Upper respiratory tract infection	10 (10.0)	6 (6.1)	8 (8.0)	9 (9.1)	10 (9.4)	33 (8.2)
Fatigue	6 (6.0)	11 (11.1)	6 (6.0)	9 (9.1)	10 (9.4)	36 (8.9)
Nasopharyngitis	7 (7.0)	5 (5.1)	10 (10.0)	8 (8.1)	9 (8.5)	32 (7.9)
Dizziness	9 (9.0)	7 (7.1)	5 (5.0)	8 (8.1)	8 (7.5)	28 (6.9)
Pruritus	4 (4.0)	9 (9.1)	2 (2.0)	5 (5.1)	10 (9.4)	26 (6.4)
Diarrhea	5 (5.0)	6 (6.1)	5 (5.0)	6 (6.1)	4 (3.8)	21 (5.2)
Insomnia	2 (2.0)	2 (2.0)	4 (4.0)	4 (4.0)	10 (9.4)	20 (5.0)
Constipation	5 (5.0)	6 (6.1)	2 (2.0)	2 (2.0)	5 (4.7)	15 (3.7)
Dry mouth	4 (4.0)	3 (3.0)	3 (3.0)	1 (1.0)	8 (7.5)	15 (3.7)
Vomiting	2 (2.0)	2 (2.0)	4 (4.0)	6 (6.1)	4 (3.8)	16 (4.0)
Back pain	4 (4.0)	3 (3.0)	2 (2.0)	5 (5.1)	4 (3.8)	14 (3.5)
Muscle spasm	3 (3.0)	3 (3.0)	2 (2.0)	7 (7.1)	1 (0.9)	13 (3.2)
Rash	4 (4.0)	3 (3.0)	5 (5.0)	3 (3.0)	0	11 (2.7)
Pain in extremity	3 (3.0)	5 (5.1)	4 (4.0)	0	2 (1.9)	11 (2.7)
Paresthesia	5 (5.0)	3 (3.0)	0	1 (1.0)	3 (2.8)	7 (1.7)
a. MedDRA high level term						

Drug-related TEAEs (as determined by the investigator):	**Placebo**	**Rotigotine (mg/24h)**				**Total Rotigotine (N=404)**
	(N=100)	**0.5 (N=99)**	**1 (N=100)**	**2 (N=99)**	**3 (N=106)**	
Subjects with ≥5% drug-related TEAEs, n (%): *(by Preferred term)*						
Any system organ class	54 (54.0)	60 (60.6)	63 (63.0)	73 (73.7)	80 (75.5)	276 (68.3)
Application and instillation site reactions[a]	5 (5.0)	22 (22.2)	17 (17.0)	34 (34.3)	36 (34.0)	109 (27.0)
Nausea	10 (10.0)	13 (13.1)	20 (20.0)	18 (18.2)	22 (20.8)	73 (18.1)
Headache	8 (8.0)	14 (14.1)	12 (12.0)	10 (10.1)	11 (10.4)	47 (11.6)
Somnolence	6 (6.0)	8 (8.1)	10 (10.0)	13 (13.1)	16 (15.1)	47 (11.6)
Fatigue	4 (4.0)	10 (10.1)	3 (3.0)	7 (7.1)	7 (6.6)	27 (6.7)
Dizziness	6 (6.0)	4 (4.0)	3 (3.0)	7 (7.1)	7 (6.6)	21 (5.2)
Pruritus	2 (2.0)	9 (9.1)	2 (2.0)	3 (3.0)	8 (7.5)	22 (5.4)
Insomnia	2 (2.0)	1 (1.0)	4 (4.0)	2 (2.0)	9 (8.5)	16 (4.0)
Dry mouth	4 (4.0)	2 (2.0)	3 (3.0)	1 (1.0)	8 (7.5)	14 (3.5)
a. MedDRA high level term						

Deaths, SAEs, and Other SAEs:	Placebo (N=100)	Rotigotine (mg/24h) 0.5 (N=99)	1 (N=100)	2 (N=99)	3 (N=106)	Total Rotigotine (N=404)
Deaths, n (%)	0	0	0	0	0	0
Subjects with SAEs, n(%)	3 (3.0)	3 (3.0)	5 (5.0)	6 (6.1)	2 (1.9)	16 (4.0)
Subjects with SAEs (by Preferred term), n (%)						
Sinus bradycardia	0	0	0	1 (1.0) [1]	0	1 (0.2) [1]
Atrial fibrillation	0	0	1 (1.0) [0]	0	0	1 (0.2) [0]
Spondylolisthesis	0	0	0	0	1 (0.9) [0]	1 (0.2) [0]
Vertigo	1 (1.0) [1]	0	0	0	0	0
Oesophageal obstruction	0	0	0	1 (1.0) [0][a]	0	1 (0.2) [0]
Abdominal hernia	1 (1.0) [0]	0	0	0	0	0
Cholecystitis	0	0	1 (1.0) [0]	0	0	1 (0.2) [0]
Hepatitis acute	1 (1.0) [0]	0	0	0	0	0
Hypersensitivity	0	1 (1.0) [0]	0	0	0	1 (0.2) [0]
Pneumonia	0	0	0	1 (1.0) [0]	0	1 (0.2) [0]
Fall	0	0	0	1 (1.0) [1]	0	1 (0.2) [1]
Lumbar spinal stenosis	0	0	0	0	1 (0.9) [0]	1 (0.2) [0]
Spinal colum stenosis	0	0	1 (1.0) [0]	0	0	1 (0.2) [0]
Intervertebral disc degeneration	0	0	1 (1.0) [0]	0	0	1 (0.2) [0]
Lung neoplasm malignant	0	0	0	0	1 (0.9) [0][b]	1 (0.2) [0]
Renal cell carcinoma stage unspecified	0	0	1 (1.0) [0]	0	0	1 (0.2) [0]
Basal cell carcinoma	0	1 (1.0) [0]	0	0	0	1 (0.2) [0]
Syncope	1 (1.0) [1]	0	0	1 (1.0) [0][c]	0	1 (0.2) [0]
Memory impairment	0	0	1 (1.0) [1][a]	0	0	1 (0.2) [1]
Transient ischaemic attack	0	1 (1.0) [0]	0	0	0	1 (0.2) [0]
Depression	0	0	0	1 (1.0) [0]	0	1 (0.2) [0]
Suicidal ideation	0	0	0	1 (1.0) [0]	0	1 (0.2) [0]

a SAE occurred while subject was on rotigotine 0.5mg/24h
b SAE occurred while subject was on rotigotine 2mg/24h
c SAE occurred while subject was on rotigotine 1mg/24h

Primary & Secondary Efficacy Outcomes:
Confirmatory hierarchical testing demonstrated that rotigotine doses of 2 and 3mg/24h were statistically significantly superior over placebo for both coprimary endpoints (IRLS sum score and CGI Item 1 [severity of illness]). The net treatment effect vs placebo observed in these 2 dose groups was -4.5 ($p=0.0002$) and -5.2 ($p<0.0001$) points in the 2 and 3mg/24h rotigotine treatment groups, respectively, for the IRLS sum score, and -0.65 ($p=0.0007$) and -0.90 ($p<0.0001$) points in the 2 and 3mg/24h groups, respectively, for the CGI Item 1 scores. Improvements in these endpoints were considered clinically relevant in the 2 highest rotigotine treatment groups. Treatment benefit was also seen for the 2 lowest doses (0.5 and 1mg/24h) compared to placebo, but the results did not demonstrate superiority over placebo. Results from the secondary efficacy variables were supportive and confirmed the robustness of the primary analysis.

Publication Reference(s) based on the study:
None at this time.

Date of report: 05-Dec-2008