Approved by UCB 02-Jun-2008

Clinical Study Summary (CSS)

CT Registry ID#: *NCT00243217 (ClinicalTrials.gov Identifier number)*
Study No.: SP709

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:
Multi-center, double-blind, randomized, placebo-controlled, six-arm, parallel-group, dose-finding trial to determine efficacy, safety and tolerability of five different transdermal doses of rotigotine in subjects with idiopathic restless legs syndrome

Investigator(s) (number only): 35

Study Center(s) (number only): 35

Length of Study:	~11 weeks	Phase of Development: 2
Date first patient enrolled:	30 Apr 2003	
Date last patient completed:	27 Feb 2004	

Abstract:
This trial was a multi-center, double-blind, randomized, placebo-controlled, six-arm, parallel-group, dose-finding trial to determine efficacy, safety, and tolerability of five 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; met the diagnosis of idiopathic RLS based on the following four essential clinical features according to the International Restless Legs Syndrome Study Group; had no previous treatment for RLS (de novo subjects or intermittently untreated subjects) or subject was not well controlled with current or previous therapy; responded previously, according to medical history information, to L-dopa therapy and/or treatment with a dopamine agonist (if pretreated); had a body mass index (BMI) between 18 and 35kg/m^2; had a minimum sum score ≥15 on the International Restless Legs Scale (IRLS) at Baseline.

The primary efficacy variable was absolute change in the IRLS sum score from Baseline to the end of the Maintenance Period. Safety was assessed by the following: adverse events (AEs), clinical laboratory parameters, vital signs including orthostatic assessment, 12-lead ECG data, physical and neurological examination, subjects' ratings of daytime sleepiness using the Epworth Sleepiness Scale (ESS), and global rating of tolerability by the investigator (CGI Item 4) and subject. Individual plasma concentrations were measured at the end of the Titration Period, and at the end of the Maintenance Period. The plasma concentration response relationship was determined as a pharmacodynamic measurement.

Rotigotine doses included were 0.5mg, 1mg, 2mg, 3mg, and 4mg/24h. Trial periods consisted of a Run-In Period (Wash-out Period) of 1 week, a Titration Period of up to 2 weeks (for subjects receiving 3mg or 4mg/24h only), a Maintenance Period of 4 weeks, a Taper Period of up to 7 days, and a 2-week Safety Follow-Up Period. The total trial duration was up to 79 days. Subjects who completed the Maintenance Period were offered the opportunity to enroll in an open-label extension trial.

Number of Patients:	**Placebo**	**Rotigotine (mg/24h)**					**All Subjects**
		0.5	**1**	**2**	**3**	**4**	
Planned, N:	50	50	50	50	50	50	300
Randomized, N:	55	52	64	49	65	56	341
Completed, n (%):	47	47	59	48	58	51	310

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	(85.5)	(90.4)	(92.2)	(98.0)	(89.2)	(91.1)	(90.9)
Number of Patients Withdrawn, n (%):	8 (14.5)	5 (9.6)	5 (7.8)	1 (2.0)	7 (10.8)	5 (8.9)	31 (9.1)
Withdrawn due to Adverse Events, n (%):	2 (3.6)	1 (1.9)[a]	3 (4.7)	0	6 (9.2)	3 (5.4)	15 (4.4)
Withdrawn for Other Reasons, n (%):	6 (10.9)	4 (7.7)	2 (3.1)	1 (2.0)	1 (1.5)	2 (3.6)	16 (4.7)
Demography:	**Placebo**	**Rotigotine (mg/24h)**					**All**
		0.5	**1**	**2**	**3**	**4**	**Subjects**
Gender (Females/Males):	34/21	38/13	44/20	28/21	48/17	37/19	229/111
Age (years), mean(SD):	58.5 (11.24)	59.2 (9.90)	57.3 (10.65)	58.4 (10.57)	57.6 (10.51)	60.1 (8.43)	58.4 (10.23)
Race, n (%):							
White	55 (100)	51 (100)	64 (100)	49 (100)	65 (100)	56 (100)	340 (100)

a. subject was randomized but did not receive trial medication

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. Overall, 46% of subjects in the placebo group and 62% of subjects in a rotigotine treatment group reported 1 or more AEs during the treatment period. Most AEs were consistent with stimulation of dopamine receptors and the use of a transdermal patch. During the treatment period, the most common AEs (incidence ≥5% in a treatment group) were nausea, application site erythema, nasopharyngitis, headache, fatigue, and application site reaction. The majority of AEs were mild or moderate in intensity. There were 8 SAEs reported by 6 subjects during the trial. All SAEs were judged by the investigator to be unlikely or not related to trial medication, with the exception of 1 event (electrocardiogram QT corrected interval prolonged) in a subject treated with rotigotine 3mg/24h. Overall, 3 placebo-treated subjects, and 12 rotigotine-treated subjects had a TEAE leading to discontinuation of trial medication. The most common AE that led to discontinuation was nausea. No subject experienced an AE of special interest (severe application site reaction, severe cardiac arrhythmia, sleep attack) during the trial. Overall, there was no evidence for an association between rotigotine treatment and QTc prolongation at doses up to 4mg/24h. No clinically relevant changes in vital signs (including orthostatic assessment), clinical chemistry, hematology, endocrine parameters, or urinalysis, or physical or neurological examination were observed. Rotigotine did not have a sedative effect based on results from the ESS. There were no mean increases in ESS scores between baseline and the end of the Maintenance Period in any treatment group.

Treatment Emergent AEs (TEAE):	**Placebo (N=55)**	**Rotigotine (mg/24h) 0.5 (N=51)**	**1 (N=64)**	**2 (N=49)**	**3 (N=65)**	**4 (N=56)**	**Total Rotigotine (N=285)**
Patients with ≥5% TEAEs, n(%):*(by Preferred term)*							
Any system organ class	25 (46)	33 (65)	31 (48)	28 (57)	49 (75)	36 (64)	177 (62.1)
Nausea	5 (9)	3 (6)	6 (9)	3 (6)	16 (25)	13 (23)	41 (14.4)
Application site erythema	0	1 (2)	6 (10)	7 (14)	7 (11)	6 (11)	
Nasopharyngitis	5 (9)	4 (8)	1 (2)	7 (14)	4 (6)	5 (9)	21 (7.4)
Headache	4 (7)	6 (12)	5 (8)	1 (2)	3 (5)	7 (13)	22 (7.7)
Fatigue	5 (9)	2 (4)	3 (5)	3 (6)	7 (11)	4 (7)	19 (6.7)

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Application site reaction	0	3 (6)	2 (3)	2 (4)	4 (6)	6 (11)	17 (6.0)
Drug-related TEAEs (as determined by the investigator):	**Placebo (N=55)**	**Rotigotine (mg/24h)**					**Total Rotigotine (N=285)**
		0.5 (N=51)	**1 (N=64)**	**2 (N=49)**	**3 (N=65)**	**4 (N=56)**	
Patients with ≥5% drug-related TEAEs, n(%):*(by Preferred term)*							
Nausea	5 (9.1)	3 (5.9)	6 (9.4)	3 (6.1)	14 (21.5)	13 (23.2)	39 (13.7)
Application site erythema	0	1 (2.0)	6 (9.4)	7 (14.3)	6 (9.2)	6 (10.7)	26 (9.1)
Application site pruritus	0	1 (2.0)	1 (1.6)	2 (4.1)	0	3 (5.4)	7 (2.5)
Fatigue	4 (7.3)	2 (3.9)	3 (4.7)	3 (6.1)	7 (10.8)	4 (7.1)	19 (6.7)
Headache	4 (7.3)	2 (3.9)	2 (3.1)	0	2 (3.1)	5 (8.9)	11 (3.9)
Dizziness	4 (7.3)	1 (2.0)	1 (1.6)	3 (6.1)	4 (6.2)	3 (5.4)	12 (4.2)
Pruritus	1 (1.8)	3 (5.9)	2 (3.1)	0	6 (9.2)	1 (1.8)	12 (4.2)
Death, SAEs, and Other SAEs :	**Placebo (N=55)**	**Rotigotine (mg/24h)**					**Total Rotigotine (N=285)**
		0.5 (N=51)	**1 (N=64)**	**2 (N=49)**	**3 (N=65)**	**4 (N=56)**	
Death, n (%):	0	0	0	0	0	0	0
Patients with SAEs, n (%):	1 (1.8)	1 (2.0)	1 (1.6)	0	3 (4.6)	0	5 (1.8)
Patients with SAEs (by Preferred term)	*n (%) [events considered drug-related by the Investigator]*						
Sympathectomy	1 (1.8) [0]	0	0	0	0	0	0
Peripheral occlusive disease	0	1 (2.0) [0]	0	0	0	0	1 (0.4) [0]
Radius fracture	0	0	1 (1.6) [0]	0	0	0	1 (0.4) [0]
Fall	0	0	1 (1.6) [0]	0	0	0	1 (0.4) [0]
Intervertebral disc protrusion	0	0	0	0	1 (1.5) [0]	0	1 (0.4) [0]
Constipation	0	0	0	0	1 (1.5) [0]	0	1 (0.4) [0]
Cholecystitis	0	0	0	0	1 (1.5) [0]	0	1 (0.4) [0]
Electrocardiogram QT corrected interval prolonged [a]	0	0	0	0	1 (1.5) [1]	0	1 (0.4) [1]
a. AE was reported as a non-serious AE, but was upgraded by the sponsor, and led to withdrawal from the trial.							
Primary & Secondary Outcomes: Superiority over placebo at rotigotine doses ranging from 1 to 4mg/24h was demonstrated for the primary efficacy variable (mean change from baseline in IRLS sum score at the end of the Maintenance Period); improvements in the IRLS sum score were clinically relevant and statistically significant. Improvements in the severity of RLS symptoms were demonstrated in the Clinical Global Impressions (CGI) Item 1 score results. Pharmacokinetic: There was a dose proportional relationship between the measured rotigotine plasma levels							

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within the dose range of 0.5 to 4mg/24h. There were no consistent differences between males and females. The mean rotigotine plasma concentrations were similar between the age groups. An analysis of IRLS sum score plasma concentration response relationship indicated a relationship between rotigotine plasma levels and IRLS sum score.
Publication Reference(s) based on the study: Oertel WH, Benes H, Garcia-Borreguero D, Geisler P, Hogl B, Saletu B et al. Efficacy of rotigotine transdermal system in severe restless legs syndrome: A randomized, double-blind, placebo-controlled, six-week dose-finding trial in Europe. Sleep Med. 2008; 9(3):228-239.
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