Clinical Study Summary (CSS)

CT Registry ID#: NCT00275236 *(ClinicalTrials.gov Identifier number)*
Study No.: SP794

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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, GmbH, A member of the UCB group

Title of Study:
A multicenter, double-blind, randomized, placebo-controlled, two-arm, parallel-group, sleep lab trial to investigate the efficacy and safety of transdermal rotigotine in subjects with idiopathic restless legs syndrome

Investigator(s) (number only): 11

Study Center(s) (number only): 11

Length of Study:	16 week maximum	Phase of Development: 3
Date first subject enrolled:	24 Nov 2005	
Date last subject completed:	21 Jul 2006	

Abstract:
SP794 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled, 2-arm parallel-group trial in subjects with idiopathic restless legs syndrome (RLS). Main inclusion criteria included the following: a diagnosis of idiopathic RLS based on the 4 essential clinical features according to the International Restless Legs Syndrome Study Group. In addition, subjects must either (1) be de novo (ie, had no previous treatment for RLS) or have had initial response to previous dopaminergic treatment, (2) have a score of ≥15 on the International Restless Legs Scale Rating Scale (indicating moderate to severe RLS) at Baseline, (3) have a score of ≥4 points on the Clinical Global Impressions (CGI) Item 1 assessment (indicating moderately ill) at Baseline, and (4) have a PLMI (periodic limb movements/total time in bed) of ≥15 based on polysomnography as assessed by the investigator. Main exclusion criteria included secondary RLS, history of sleep disturbances, and symptomatic orthostatic hypotension.

The primary efficacy outcome was assessed by the reduction of the Periodic Limb Movements Index (PLMI) at the end of the Maintenance Period compared to Baseline. The following secondary efficacy variables were measured as change from Baseline at the end of the Maintenance Period: PLMSAI (Periodic Limb Movements during Sleep Arousal Index; PLMs during sleep with arousals/total sleep time), Sleep efficiency (%; sleep time/TIB), IRLS sum score, CGI Item 1 (severity of illness), and MOS Sleep Scale-Adequacy Subscale.

Safety was assessed by the following: adverse events (AEs), changes in laboratory tests, changes in vital signs, 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 at the end of the Maintenance Period, changes in the Self-Rating Depression Scale, Global Subject Rating of Tolerability, and Clinical Global Impressions (CGI) Item 4.

Subjects were enrolled and randomized to receive placebo or rotigotine in a 2:1 fashion. All subjects began the 3-week Titration Period at a daily dosage of rotigotine 1mg/24h or placebo. Subjects were up-titrated weekly in 1mg/24h increments to their optimal dose, with a maximum dose of rotigotine 3mg/24hr or placebo. The maximum length of titration was 21 days (+3 days). When the Titration Period was complete, or both the subject and investigator decided that the dose was optimal for the subject, the subject remained at that dose

and entered the 4-week Maintenance Period. Subjects who completed the 4-week Maintenance Period and a 7-day Taper Period were eligible to participate in an open-label extension trial. Subjects who did not complete the 4-week Maintenance Period or who chose not to participate in the open-label extension trial completed a 30-day Safety Follow-Up Period.

Number of Subjects:	**Placebo**	**Rotigotine**	**Total**
Planned, N:	20	40	60
Enrolled/Randomized, N:	21	46	67
Completed, n (%):	20 (95.2)	41 (89.1)	61 (91.0)
Number of Subjects Withdrawn, n (%):	1 (4.8)	5 (10.9)	6 (9.0)
Withdrawn due to Adverse Events, n (%):	1 (100.0)	2 (40.0)	3 (50.0)
Withdrawn for Other Reasons, n (%):	0	3 (60.0)	3 (50.0)
Demography:			
Gender (Females/Males):	14/7	35/11	49/18
Age (years), mean (SD):	55.2 (10.6)	60.8 (9.4)	59.1 (10.1)
Race, n (%):			
White	21 (100)	46 (100)	67 (100)

Safety Outcomes:
Rotigotine was well tolerated in this trial. Most AEs were consistent with stimulations of dopamine receptors and use of a transdermal patch. The most frequently occurring AEs were nausea, headache, and application site reactions. All application site reactions were mild or moderate in severity and none led to discontinuation from the trial. There was one treatment-emergent serious adverse event (SAE) during the trial which occurred during the Safety-Follow-up Period. Overall, 2 rotigotine-treated subjects and 1 placebo-treated subject discontinued from the trial because of an AE. Overall, there is no evidence for an association between rotigotine treatment and ECG abnormalities or changes at doses up to 6.75mg/day. 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.

A summary of AEs is provided below:

Treatment Emergent AEs (TEAE):	**Placebo (N=21)**	**Rotigotine total (N=46)**
Subjects with ≥5% TEAEs, n (%): (by Preferred term)		
Any system organ class	12 (57.1)	34 (73.9)
Nausea	1 (4.8)	10 (21.7)
Headache	4 (19.0)	9 (19.6)
Application and instillation site reactions	1 (4.8)	8 (17.4)
Somnolence	2 (9.5)	6 (13.0)
Fatigue	2 (9.5)	4 (8.7)
Constipation	0	3 (6.5)
Nasopharyngitis	0	3 (6.5)
Dizziness	0	3 (6.5)
Insomnia	0	3 (6.5)

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Drug-related TEAEs in ≥5% of Subjects (as determined by the investigator), n (%) (by Preferred term):	**Placebo (N=21)**	**Rotigotine total (N=46)**
Any system organ class	9 (42.9)	29 (63.0)
Nausea	1 (4.8)	10 (21.7)
Constipation	0	3 (6.5)
Application and instillation site reactions[a]	1 (4.8)	8 (17.4)
Fatigue	2 (9.5)	4 (8.7)
Headache	3 (14.3)	8 (17.4)
Somnolence	2 (9.5)	5 (10.9)
Dizziness	0	3 (6.5)
Insomnia	0	3 (6.5)
a. High Level Term		
Death, SAEs, and Other SAEs:	**Placebo**	**Rotigotine total**
Death, n (%):	0	0
Subjects with SAEs, n (%):	0	1 (2.2)[a]
Subjects with SAEs (by Primary System Organ Class)		
Osteoarthritis	0	1 (2.2)[a] [0]

[a] Event occurred during Safety Follow-up Period

Primary & Secondary Efficacy Outcomes:
Superiority of rotigotine over placebo was demonstrated at a significance level of 0.025 for the primary efficacy variable (reduction from Baseline in the PLMI at the end of the Maintenance Period). The results of the IRLS sum score (secondary variable) are consistent with the primary analysis. Twenty-six percent (26%) of rotigotine-treated subjects had a score of 0, reflecting they did not have any RLS symptoms at the end of the Maintenance Period. The majority of rotigotine-treated subjects (73%) achieved a clinically normal level of ≤2 on the PLMASI (arousal index) compared to 25% of placebo-treated subjects. Overall, the efficacy results in this trial were positive with respect to the objective measures (eg, PLMI); non-PLM parameters related to sleep (ie, non-movement secondary efficacy parameters) did not show pronounced changes.

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

Date of report: 05-Dec-2008