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ASSESSMENT REPORT
FOR
NEUPRO

International Nonproprietary Name:
rotigotine

Procedure No. EMEA/H/C/626/II/0019

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. Introduction

Restless Legs Syndrome is best described as a neurological sensory-motor disorder characterized by four essential diagnostic criteria defined by the International Restless Legs Syndrome Study Group (IRLSSG) in 1995 and updated in 2003.

Patients report an irresistible leg movement that is often accompanied by creeping sensations deep in the limbs. The symptoms of RLS are not confined to the legs, but can also occur in the upper limbs. The majority of symptoms of RLS occur in the evening and at night. Lying down in bed is associated with increased paresthesia and an irresistible urge to move, often accompanied by periodic limb movements which interfere with sleep onset and with consolidation of sleep.

Restless Legs Syndrome is one of the most frequent neurological diseases, with an estimated prevalence of 7% to 11% of the general population.

Neupro (rotigotine) is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease (PD) as monotherapy (i.e. without levodopa) or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or 'on-off' fluctuations).

Rotigotine is a non-ergolinic dopamine agonist. It has a high in vitro affinity for all dopamine receptor subtypes which is particularly high for the D3 receptor, about 10-fold less for the D2 and about 100-fold less for the D1 receptor. It also has high intrinsic (agonistic) activity on all dopamine receptor subtypes which, again, is particularly high for the D3 subtype.

The currently approved formulations are presented as 10 cm^2, 20 cm^2, 30 $cm^2$and 40 cm^2 transdermal patches containing respectively 4.5 mg, 9.0 mg, 13.5 mg and 18.0 mg of rotigotine, and designed to release respectively 2 mg, 4 mg, 6 mg and 8 mg of rotigotine per 24 hours.

This variation refers to an extension of the therapeutic indication to include *'symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (RLS) in adults'.*

In the proposed extension of indication, the starting dose is 1 mg/24 hours, thus introducing new dosage of rotigotine. Depending on the individual patient response, the dose may be increased in weekly increments of 1 mg/24 hours to a maximal dose of 3 mg/24 hours.
An extension application is therefore submitted in parallel to add 2 new strengths 1mg/24 h and 3mg/24 h of rotigotine (EMEA/H/C/626/X/20). These formulations are presented as 5cm^2, 15 cm^2 transdermal patches containing respectively 2.25mg and 6.75 mg of rotigotine and designed to release respectively 1mg and 3 mg of rotigotine per 24 hours.

2. Non clinical aspects

The pharmacokinetic and toxicological results from animal studies, supportive of the approved patches have been previously assessed at the time of the initial application for Neupro. The dose of 18 mg (40 cm2 patch size, i.e 8 mg/24h), maximum therapeutic dose observed for the early stage Parkinson patients, was used as basis to calculate the safety margins of rotigotine. An update of these calculations was made at the time of the application to extend the indication to the advanced stage Parkinson patients (EMEA/H/C/626/II/03).

Within this variation application, a new calculation of the toxicological safety margins (see Table 1) is provided for the proposed maximum human dose of 6.75 mg for the treatment of RLS based on the mean maximum rotigotine plasma concentration (i.e 0.58 ng/mL) and mean AUC value (10.62 h.ng/mL).

Table 1 Safety ratios at No-Observed-Effect Levels (NOELs) and Cmax and AUC in human plasma at the maximum therapeutic dose

Maximum therapeutic dose	**Dose**	**Cmax**	**AUC(daily)**
	15 cm^2 3 mg/24 hours	0.58 ng/mL	10.62 h ng/mL
Repeat dose toxicity studies	**NOEL[a] or MTD[b](mg/kg)**	**Safety margin Cmax**	**Safety margin AUC**
Rat, 6 months	0.5[a]	4	2
Monkey, 12 months	1[a]	5-6	3-4
Carcinogenicity studies			
Mouse	30[b]	46	36
Rat	3[b]	12	10
Reproductive and developmental studies			
Mouse, Segment II	30[a] fetus	114	-
Rat, Segment I	>15[a] male	>90	-
Rat, Segment I	1.5[a] female	7	-
Rat, Segment II, teratogenicity	1.5[a] fetus	8	8
Rabbit, Segment II	25[a] (fetus)	859	783

- = insufficient samples available for AUC calculation

At doses above the NOEL, the most prominent systemic effects, such as effects on food/water consumption and body weight, are mainly related to the pharmacodynamic, dopamine agonistic effects in healthy animals and/or the well-known influence of dopamine agonists on sex hormone (e.g. prolactin) secretion.

Overall, rotigotine did not result in any target organ toxicity. With respect to the toxicological data and relevant non-clinical findings, the CHMP concluded that the safety ratios compared to the maximum intended dose in RLS patients (3 mg) were acceptable.

Ecotoxicity/environmental risk assessment

The submitted ERA included a phase II tier A analysis where the MAH concluded that no additional risk for the aquatic environment will result from the additional environmental exposure to rotigotine due to treatment of RLS patients because the trigger limits of PEC:PNEC ratios will not be exceeded as the maximum intended dose for RLS (6.75 mg) is lower than those previously approved for treatment of early and advanced PD patients (18 and 36 mg).

However, the CHMP requested the MAH to further evaluate the impact occurring on the penetration factor (Fpen) by extending the indication to RLS patients and on all subsequent ERA consequences (PECsurfacewater, PECsoil and PEC:PNEC ratios).

Based on the available data, the CHMP concluded that the risk for the aquatic compartment was acceptable, given that the calculated PEC/PNEC ratio was 0.35. However, the CHMP requested the MAH to complete the assessment of the soil compartment and to further address the calculation of the penetration factor (Fpen) refinement as part of a follow-up measure. The CHMP also requested a bioconcentration study in fish for which the MAH committed to.

3. Clinical aspects

The clinical development program to support the extension of indication of Neupro to symptomatic treatment of moderate to severe idiopathic RLS consisted of 8 clinical trials (see Table 2).

The clinical trials were conducted in accordance with GCP as stated by the MAH.

Table 2 Summary of the 8 clinical trials performed in patients with RLS.

Study number	Study design	Rotigotine dose/24h	Objective
SP666	MC, RD, DB, PC, parallel groups, fixed dose	1.125 mg - 4.5 mg dosing: 1 week	proof-of-concept and to analyze the dose-response relationship of rotigotine
SP709	MC, RD, DB, PC, parallel groups, fixed dose	1.125 mg - 9 mg 4 weeks maintenance	dose finding trial
SP710	open-label extension trial of SP709	2.25 mg - 9 mg	assess safety and tolerability of rotigotine; ongoing
SP790	MC, RD, DB, PC, parallel fixed dose	2.25 mg - 6.75 mg 6 months maintenance	pivotal efficacy study
SP792	MC, RD, DB, PC, parallel fixed dose	1.125 mg - 6.75 mg 6 months maintenance	pivotal efficacy study
SP791	Open, optimal dose	1.125 mg - 6.75 mg	open label extension trial of studies SP790 and SP794; ongoing
SP793	Open, optimal dose	2.25 mg - 6.75 mg	open label extension trial of studies SP792; ongoing
SP794	MC, RD, DB, PC, parallel groups, optimal dose	2.25 mg - 6.75 mg 4 weeks maintenance	demonstrate efficacy of rotigotine based on the Periodic Limb Movement Index (PLMI = PLMs/total time in bed [TIB]) as measured by polysomnography (PSG).

MC: multicentre, RD: randomised, DB: double blind, PC: Placebo controlled

Study SP666 was a proof of concept trial. Studies SP709 and SP710 were phase II trials and studies SP790, SP791, SP792, SP793 and SP794 were phase III trials.

Furthermore, additional pharmacokinetic and pharmacodynamic studies (SP871, SP651, SP864, SP861 and SP862) have been conducted to evaluate the influence of the application site on the bioavailability of rotigotine, the potential electrocardiographic effects of rotigotine transdermal system and the interactions with oral contraceptives (fixed combination of ethinylestradiol and levonorgestrel) and CYP2C19 inhibitor (omeprazole).

Pharmacokinetics

- **Absorption**

Studies **SP651** (18 mg/40 cm² single patch versus 2 x 9 mg/20 cm² patches) and **SP871** (6.75 mg/15 cm² single patch versus 4.5 mg/10 cm² + 2.25 mg/5 cm² patches) were performed to compare the relative bioavailability of one patch versus two patches of the same total dose, at 6 different application sites.

Study SP871, SP651

Study design

These studies were 2-way crossover trials to investigate the relative bioavailability of administration of one rotigotine patch compared to combined administration of two patches of the same total dose. The secondary objective was to characterise the influence of application site on the bioavailability of rotigotine at steady state.

Study SP651 (with the 18 mg dose) was performed in patients with advanced PD, and study SP871 in healthy subjects, using a 6.75 mg dose.

Subjects were brought in steady state with single patches for the bioequivalence part of the study. Then, for 6 following days, patches were applied in a cross-over design (Days 21 and 22) in which subjects received one and two patches and application sites were varied (shoulder, upper arm, abdomen, flank, hip, and thigh). Blood samples were drawn at baseline, and 2, 4, 6, 8, 12, 16, and 20h after patch application.

Results

Plasma exposure after either two patches or one patch of the same total dose was similar in both studies. The 90% CI of the $AUC_{0\text{-}24h,ss}$ ratio was 90.5-100.5 (SP871), and 93.7-105.7 (SP651), indicating bioequivalence.

Plasma exposure is the lowest after application on thigh/abdomen, and the highest after application on the shoulders.

- **Interaction studies**

Study SP861

Study design

This was a randomized, double-blind, placebo-controlled, crossover, multiple-dose trial, performed to investigate the interaction with a fixed combination of ethinylestradiol and levonorgestrel (oral contraceptive) in 36 healthy young females.

Following a 2-month Run-In Period on oral hormonal contraception, subjects received either rotigotine patch (Treatment A) or placebo patch (Treatment B) for 2 treatment periods. Each period lasted 28 days during which patch medication was administered on Days 1 to 13, and the oral contraceptive on Day 1-21, followed by a pill-free week. Rotigotine patch dose was uptitrated from 4.5 mg to 6.75 mg within 3 days.

Plasma levels of rotigotine, ethinylestradiol + levonorgestrel were measured at Day 1 (pre-dose) and Day 13. Serum levels of intrinsic hormones **[**estradiol (ES), luteinizing hormone (LH), and follicle stimulating hormone (FSH)] were collected at Day 10, Day 13, and Day 14 before administration of trial medication, and intrinsic progesterone and estradiol were measured at Day 19, Day 20, and Day 21 before administration of the oral hormonal contraceptive.

Results

All subjects completed the study.

Rotigotine had no significant effect on plasma levels of ethinylestradiol and levonorgestrel.

The administration of rotigotine patches had no influence on contraceptive activity of the fixed combination of ethinylestradiol and levonorgestrel as the progesterone levels remained low after either placebo or rotigotine treatment (<1.3 ng/mL during Day 19 to Day 21). Moreover, ES, FSH and LH levels were low and similar for placebo and rotigotine treatment-arms, indicating that ovulation was unlikely to occur.

SP862

Study design

This was an open-label sequential trial, performed to investigate the interaction with omeprazole (CYP2C19 inhibitor).

Rotigotine patches were administered for 14 days. Subjects were up-titrated to 9.0mg/day (20cm^2) within 3 days and remained on that dose until Day 12. Subjects received omeprazole capsules (40mg) once daily in the mornings of Days 7 - 12. At Day 13-14, rotigotine was down-titrated. Samples were drawn at Day 6 and 12, in a time frame of 24 hrs.

Results

Fifty-four healthy males (all extensive metabolizers for CYP2C19) enrolled in this trial; Fourteen subjects were withdrawn because of manufacturing defects of the patches, and 2 subjects withdrew due to AEs [orthostatic hypotension (probably related) and hepatic enzyme increment (not related)]. PK data were available for 37 subjects.

There were no relevant changes in plasma concentrations of rotigotine (neither conjugated nor free) or the N-desalkyl metabolites.

- **Dose – response**

The dose-exposure relationship is linear for dose range between 1.125-9 mg (0.5-4 mg/24h, nominal dose).
There was no clear dose-response relationship, as there is a considerable overlap of plasma concentrations achieved after the different dose levels.

- **Discussion on pharmacokinetics**

From the pharmacokinetic (PK) data obtained in several Phase II and Phase III studies performed in RLS patients, the plasma exposure in RLS was similar as reported before in PD patients (who are in general older) and young healthy volunteers, confirming that PK of rotigotine is not largely influenced by differences in age, gender and body weight. There was no clear dose-response relationship for efficacy in RLS treatment in the recommended dosing regimen.

Though CYP2C19 is a relevant pathway in-vitro, inhibition of this pathway did not lead to clinical relevant changes in rotigotine exposure in-vivo when administered concomitantly with omeprazole.

Rotigotine had no significant effect on PK of ingredients of the contraceptive pill (in this case ethinylestradiol 0.03 mg + levonorgestrel 0.15 mg), and neither on the contraceptive activity on the intrinsic hormones, and this form of contraception can be safely used in combination with rotigotine.

Results from a pooled analysis of three studies where the effect of application site on plasma exposure was studied, confirmed earlier conclusions that the exposure could vary significantly from day-to-day when changing application site, and that exposure is the lowest at abdomen and thighs.

A linear plasma exposure-dose relationship has been established for dose range 0.5-4 mg/24h thus including the proposed dosage of 1mg/24h and 3 mg/24h.

Pharmacodynamics

- **Study SP864**

Study design

SP864 was a double-blind, randomized, placebo- and positive-controlled, parallel-group trial to assess the potential electrocardiographic effects of rotigotine transdermal system up to 54.0 mg/day.

The study was performed in 130 male and female patients with advanced-stage idiopathic Parkinson's disease who were assigned to receive treatment with either rotigotine patch at doses from 9.0 mg/day to 54.0 mg/day or placebo patch.

In addition, within the placebo group, subjects were randomized to the sequence of receiving either placebo saline intravenous (iv) solution or moxifloxacin iv solution (positive control) on Day 32 and 39 in a crossover design (50% of subjects in the placebo group received positive control on Day 32 [Sequence 1] the other 50% on Day 39 [Sequence 2]). This treatment was in addition to treatment with the placebo patch. All subjects in the rotigotine treatment group received placebo saline iv solution on both Day 32 and Day 39.

Based on the 24-hour continuous drug delivery system, ECGs were recorded during day and night time, starting on Days -3, -2, 14, 21, 28, 35 and 42, and were followed by daytime serial 12-lead ECG recordings on Days -2, -1, 15, 22, 29, 36 and 43. Daytime serial 12-lead ECG recordings without preceding overnight recordings were recorded on Days 32 and 39. Blood samples for determination of rotigotine concentrations in plasma were drawn on Days 14/15, 21/22, 28/29, 35/36 and 42/43. Safety and tolerability were assessed throughout the trial.

Primary endpoints

The primary electrocardiographic endpoints were:
- QTc comparison of rotigotine vs. placebo (parallel-group comparison).
- QTc comparison of positive control vs. placebo (cross-over comparison).

Results

Moxifloxacin, the positive control, prolonged QTc as expected. There was no evidence of an association between rotigotine treatment (up to 54.0 mg/day) and QTc prolongation. Exposure to rotigotine was proportional to the dose administered and in accordance with previous trials. There was no correlation between the plasma concentrations of unconjugated rotigotine and changes in QTc. Up to 54.0 mg/day of rotigotine was shown to be safe and well tolerated after administration over 52 days in male and female subjects with Parkinson's disease.

Overall, this study was well designed and showed no prolongation of the QTc after treatment with rotigotine up to 54 mg/day.

Clinical efficacy

Eight clinical trials were performed to assess the safety and efficacy of rotigotine in patients with RLS. Idiopathic RLS was diagnosed using the International Restless Legs Syndrome Study Group (IRLSSG) criteria.

In total 1309 subjects with RLS were treated with rotigotine. In the clinical studies the IRLS and/or the CGI Item 1 were used as primary efficacy assessment and to define the primary endpoints. These scales are internationally recognized. Studies SP790 and SP792 are considered the main efficacy studies.

The following 10 items were assessed on the IRLS (International Restless Leg Syndrome) scale: 1. Global severity rating of RLS in legs and arms; 2. Urge to move; 3. Relief by walking; 4. Sleep disturbances due to RLS; 5. Fatigue and somnolence due to RLS during the day; 6. Global severity rating of RLS; 7. Frequency of symptoms; 8. Severity of symptoms during an average day (24 hours), if present; 9. Impact of symptoms on daytime activities (family, home setting, contacts to friends, job); 10. Impact of symptoms on mood (anger, dejection, sadness, anxiousness, irritation).

In all items, scores ranged from 0 (not present) to 4 (severe). A sum score across all 10 items was calculated for analysis which varied between 0 (no RLS symptoms present) to 40 (maximum severity in all symptoms).

The following ranges were used to determine severity categories: 0=none, 1 to 10=mild, 11 to 20=moderate, 21 to 30=severe, 31 to 40=very severe.

Scores for CGI (Clinical Global Impression) Item 1 range from 0 to 7 as follows: 0=not assessed, 1=normal, not ill at all, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill.

- Dose-response studies

Table 3 Summary of the study characteristics

Study number	**Study design**	**Rotigotine dose/24h (n)**	**Duration**	**Clinical endpoints**
SP666 Proof of concept trial	MC, RD, DB, PC, parallel groups, fixed dose N=63 (randomized) N=63 (SAS) N=63 (FAS) N=58 (PPS) Rotigotine: n= 49 Placebo: n=14 Males and females	1.125 mg (17) 2.25 mg (13) 4.5 mg (19) placebo (14)	7±4 days washout, dosing on day 1-7.	Absolute change from baseline to end of treatment (difference) in the total score of the IRLSSG scale.
SP709 Dose finding trial	MC, RD, DB, PC, parallel groups, fixed dose N=341 (randomized) N=340 (SAS) N=333 (FAS) N=291 (PPS) Rotigotine: n= 286 Placebo: n=55 Males and females	1.125 mg (52) 2.25 mg (64) 4.5 mg (49) 6.75 mg (65) 9 mg (56) placebo (55)	-7 day run-in period -2 week titration period* -4 weeks maintenance period -7 days taper off period -2 week follow up period	Absolute change from baseline to end of treatment (difference) in the total score of the IRLS scale.

* for subjects receiving 6.75mg or 9.0mg only; FAS: full set analysis, PPS: per protocol set

Studies SP666 and SP709

METHODS

Objectives

The main objectives of the two phase II studies were to show proof-of-concept and analyze the dose-response relationship of rotigotine in subjects with advanced stage of idiopathic RLS (study SP666)

and to investigate the efficacy of five different dosages of rotigotine in RLS patients (dose finding study SP709).

Study design

Multicentre, randomized, double-blind placebo-controlled, parallel design studies.

Study Participants

Study SP666

Patients had to have an initial response to previous dopaminergic treatment for RLS or had no previous dopaminergic treatment. Subject had to have a minimum score ≥ 5 in the sum score of the IRLSSG rating scale at the first visit under L-dopa treatment or a minimum score ≥ 10 in untreated subjects. At visit 2, after completion of a wash out period when pre-treated and before start of treatment with trial medication, all subject scored ≥ 10 in the sum score of the IRLS scale (indicating moderate to severe RLS). In addition, all subject showed daytime symptoms of restless legs as defined by a score ≥ 3 in the scale 'severity of RLS during the day' at the first and at the second visit.

Study SP709

Subjects had to have a minimum score ≥ 15 (indicating moderate to severe RLS) in the sum score of the IRLSSG rating scale at baseline. Patients had no previous treatment for RLS or the subject was not well-controlled with current or previous therapy. However, previous treated patients had responded previously, according to medical history information, to L-dopa therapy and/or treatment with a dopamine agonist (if pre-treated). Subjects were excluded from the trial if they had secondary RLS; a history of sleep disturbances; other central nervous diseases and any other psychotropic medications; previous treatment with dopamine agonists within a period of 4 weeks prior to enrolment

Treatment study arms

In study SP666 (four study arms), subjects were up titrated to a fixed dose of 1.125, 2.25, or 4.5 mg rotigotine or received placebo treatment.

In study SP709 (six study arms), subjects were up titrated to a fixed dose of 1.125 mg, 2.25 mg, 4.5 mg, 6.75 mg or 9 mg rotigotine or to placebo treatment. Subjects who were treated for RLS had to complete a wash out period of 7 days.

Primary endpoint

The primary efficacy endpoint was absolute change in the IRLS sum score from baseline to the end of the maintenance period (difference).

RESULTS

In study SP666, 63 male and female patients (mean age 58.3±8.8, range 37-74) with idiopathic RLS participated in the study.

In study SP709, 341 male and female patients (mean age 58.3±8.8, range 37-74) with idiopathic RLS participated in the study.

Rotigotine has a linear relationship between dose and unconjugated rotigotine plasma concentrations in patients with idiopathic restless legs syndrome. There were no differences between different age groups (≤65 years and ≥65 years). Results are presented in Tables 4, 5 and 6:

Table 4: Study SP666; Total score of the IRLSSG rating scale: baseline scores and scores as change from baseline for the Full Analysis Set (FAS) and Per Protocol Set (PPS)*

	Placebo	**1.125 mg**	**2.25 mg**	**4.5 mg**
FAS (n=63)	N=14	N=17	N=13	N=19
baseline	25.0 ± 5.0	26.1 ± 5.3	26.6 ± 5.0	25.9 ± 5.4
Δ baseline	-7.4 ± 7.4	-10.6 ± 9.2	-12.8 ± 8.5	-15.7 ± 9.4
PPS (n=58)	N=12	N=15	N=12	N=19
baseline	24.4 ± 4.4	27.5 ± 3.9	26.3 ± 5.1	25.9 ± 5.4
Δ baseline	-8.5 ± 7.2	-11.9 ± 8.9	-13.3 ± 8.7	-15.7 ± 9.4

*Results are given as mean ± SD.

Table 5: Study SP666; Comparison between groups

	LS means ± SEM	**95% CI**	**P-value**
FAS (N=63)			
Placebo – 1.125 mg rotigotine	2.5 ± 3.0	-3.5; +8.4	0.4117
Placebo – 2.25 mg rotigotine	4.3 ± 3.2	-2.0; +10.6	0.1786
Placebo – 4.5 mg rotigotine	7.7 ± 2.9	+2.0; +13.5	0.0095
PPS (N=58)			
Placebo – 1.125 mg rotigotine	1.3 ± 3.3	-5.2; +7.9	0.6835
Placebo – 2.25 mg rotigotine	3.6 ± 3.4	-3.2; +10.4	0.2889
Placebo – 4.5 mg rotigotine	6.3 ± 3.0	+0.2; +12.4	0.0446

Table 6: Study SP709; IRLS sum score at baseline and end of maintenance period*

Study SP709	**n**	**Baseline**	**End of MP**	**Mean change ± *SD***	**95% CI**	**p-value**
Placebo	53	28.0 ± 6.25	18.7 ± 10.57	-9.3 ± 9.6	-	-
Rotigotine 1.125 mg/day	50	27.8 ± 6.01	17.3 ± 9.74	-10.5 ± 9.2	-1.2 (-4.96; 2.28)	0.23338
Rotigotine 2.25 mg/day	64	28.2 ± 5.43	13..9 ± 10.08	-15.3 ± 10.0	-6.0 (-9.26; -2.43)	0.0004
Rotigotine 4.5 mg/day	49	28.0 ± 5.38	12.2 ± 9.12	-15.7 ± 9.5	-6.4 (-10.10; -2.81)	0.0003
Rotigotine 6.75 mg/day	64	27.4 ± 6.12	10.1 ± 8.56	-17.3 ± 10.5	-8.0 (-11.73; -4.90)	<0.0001
Rotigotine 9.0 mg/day	53	28.2 ± 6.56	13.3 ± 10.07	-14.9 ± 10.3	-5.6 (-9.09; -1.95)	0.0013

*with p-values and 95%CI after comparison of treatment with placebo. (ANCOVA of FAS with LOCF).

Results of study SP666 showed a dose-response relationship of rotigotine in comparison to placebo, i.e with increasing dose there was a greater decrease on the IRLSSG. The proposed doses (up to 6.75 mg) showed a statistically significant improvement.

- **Main studies**

Studies SP790 and SP792

METHODS

Objectives

The main objective of the studies SP790 and SP792 was to assess the efficacy of rotigotine for the treatment of RLS.

Study design

Both studies were multi-centre, randomized, placebo-controlled and double-blind with parallel groups.

Study Participants

Males and females were included in these trials. Idiopathic RLS was diagnosed using the International Restless Legs Syndrome Study Group (IRLSSG).

Patients had to have an initial response to previous dopaminergic treatment for RLS or had no previous dopaminergic treatment. At baseline, that is after the run-in period, subject had to have a score of ≥15 on the IRLSSG (indicating moderate to severe RLS). In addition, at baseline patients had to have a score ≥4 points on the Clinical Global Impressions 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 or other central nervous diseases.

The following concomitant medications/treatments were not permitted during the course of these trials: neuroleptics, hypnotics, antidepressants, anxiolytics, benzodiazepines, anticonvulsive therapy, L-dopa, budipine, dopamine agonists, opioids, MAO-inhibitors, COMT inhibitors, sedative antihistamines, dopamine antagonist antiemetics (except domperidone) and psycho stimulatory drugs.

Treatment study arms

Study SP790 was performed in Europe and consisted of four study arms: rotigotine 2.25 mg, rotigotine 4.5 mg, rotigotine 6.75 mg and placebo.

Study SP792 had almost the same study design as study SP790; with the inclusion of an additional study arm of rotigotine 1.125 mg/day.

A 7-day run-in period was followed by a 3 weeks titration period. Back titration was allowed once in the titration period in case of AEs suspected to be related to dopaminergic stimulation. Hereafter, a 6 months maintenance period followed. At the end of the trial a 7 days taper off period was scheduled.
Subjects were randomized centrally by an interactive response system (IVRS). Subjects were randomized in a ratio 1:1:1:1 (active:placebo) ratio for study SP790 and in a ratio of 1:1:1:1:1 (active:placebo) for study SP792. Subjects and investigators were blinded to trial medication and dose. Rotigotine and placebo-matched patches and their accompanying packaging were identical in appearance.

Sample size

For the IRLS sum score and the CGI, a 2-group t-test with a 0.025 1-sided significance level will have 92% power to detect superiority of rotigotine over placebo, assuming a difference in means of 5.0 points towards rotigotine and that the common standard deviation is 10.0, when the sample size in each group is 95 subjects.
The power to demonstrate superiority of rotigotine 6.75mg vs. placebo at the first step of the hierarchical analyses then is at least 85%. The conditional power at each following step will also be 85% if the step is reached. Consequently, the overall power of the trial to demonstrate superiority of all 3 rotigotine doses (6.75, 4.5, and 2.25mg/day rotigotine) vs. placebo will result in at least 61%. Study SP790 showed that approximately 3% of randomized subjects could not be used for the analysis. Therefore, a sample size of 100 subjects in each group should be randomized, to ensure that 95 subjects per treatment group are valid for the analyses.

Statistical methods

The different rotigotine doses were compared with placebo to demonstrate superior efficacy on the IRLS and the GCI Item 1 score. An analysis of covariance (ANCOVA) was performed for the changes from baseline to end of the maintenance period with dose level or placebo as the main factor, baseline as a covariate. The reports contain descriptive statistics, 95% confidence intervals, and p-values.

Primary endpoints

Primary clinical endpoints were the absolute change from baseline to end of the maintenance period in the IRLS sum score and the CGI Item 1 (severity of illness score). For the IRLS sum score, a decrease of 4 points (indicating improvement) was considered clinically relevant after a 6-months treatment period.

Secondary endpoints

Secondary endpoints were: IRLS responders (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 responders (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, change from baseline in RLS-6 Rating Scales at the end of the maintenance period, and the Global Subject Rating of Efficacy.

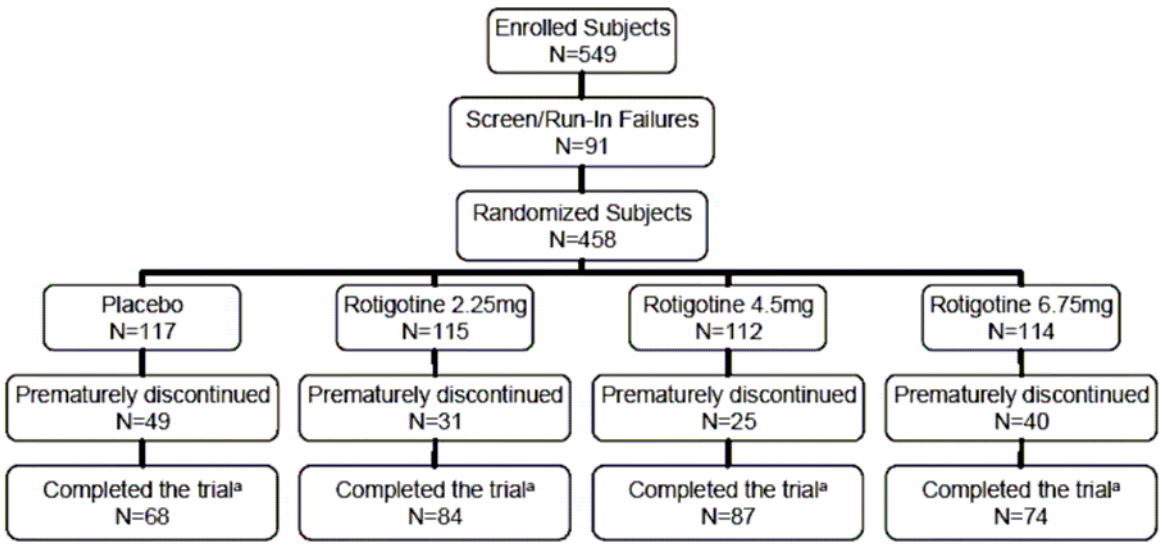
RESULTS

Recruitment/participant flow/number analysed

The flow charts (Figures 1 and 2) give a summary of subject disposition of studies SP790 and SP792. The main reason for discontinuation was adverse events. 6 % of placebo-treated subjects and 18% of all rotigotine-treated subjects with RLS had an adverse event that led to discontinuation of trial medication.

Study SP790

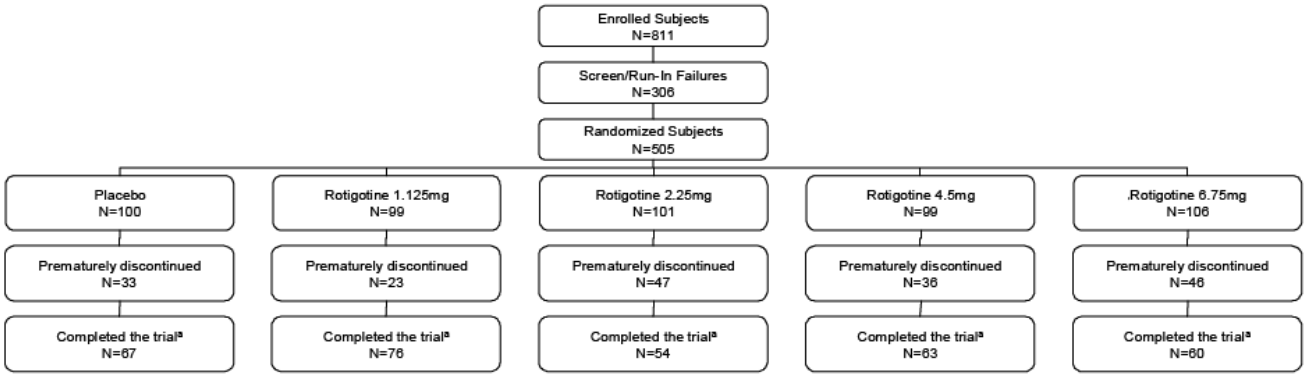
Figure 1



a. Defined as subjects who completed all Maintenance Period visits.

Study SP792

Figure 2



a Defined as subjects who completed all Maintenance Period visits.

Table 7 Summary of the analysis population

			Rotigotine (mg/day)									
	Placebo		**1.125 mg**		**2.25 mg**		**4.5 mg**		**6.75 mg**		**Total**	
	SP790	SP792	SP790	SP792	SP790	SP792	SP790	SP792	SP790	SP792	SP790	SP792
Population	**117**	**100**	**-**	**99**	**115**	**101**	**112**	**99**	**114**	**106**	**458**	**505**
Safety Set	117 (100)	100 (100)	-	100 (99)	115 (100)	100 (99.0)	112 (100)	99 (100)	114 (100)	106 (100)	458 (100)	504 (99.8)
Full Analysis Set	114 (97.4)	99 (99.0)	-	98 (99.0)	112 (97.4)	99 (98.0)	109 (97.3)	95 (96.0)	112 (98.2)	103 (97.2)	447 (97.6)	494 (97.8)
Per Protocol Set	99 (84.6)	79 (79.0)	-	80 (80.8)	99 (86.1)	78 (77.2)	95 (84.8)	79 (79.8)	94 (82.5)	78 (73.6)	387 (84.5)	394 (78.0)
Completer Set	60 (51.3)	51 (22.0)	-	64 (64.6)	79 (68.7)	36 (35.6)	77 (68.8)	48 (48.5)	73 (64.0)	48 (45.3)	289 (63.1)	247 (48.9)

*All values are n (%).

Baseline data

Study SP790

The mean age of subjects in the safety set was 57.6 years; with the majority (66%) of subjects <65 years old. The majority of subjects were female (placebo: 69% subjects, 2.25mg rotigotine: 73% subjects, 4.5mg rotigotine: 76% subjects, 6.75mg rotigotine: 73% subjects), and 99% of subjects were white. There were no notable differences in demographic characteristics between the safety set and the full analysis set and the per protocol set.

In the safety set, the mean number of years since subjects were diagnosed with RLS was 3.1 years. Overall, 28% of subjects were considered de novo (defined as not having received any RLS medication in the last 3 years). For subjects who were pre-treated, the mean number of years since the start of RLS drug therapy was 3.7 years. There were no differences across treatment groups with respect to RLS diagnosis information in either the safety set and the full analysis set. At baseline, the mean IRLS sum score was 28.1 for subjects in the placebo group, and ranged from 28.0 to 28.2 across the rotigotine treatment groups. At baseline, the mean CGI Item 1 (severity of illness) score was 5.0 for subjects in the placebo group, and ranged from 5.0 to 5.1 across the rotigotine treatment groups. Overall, there were no important differences between treatment groups in the severity of disease at baseline.

Overall, 76% of subjects had concomitant disease present at screening. The most concomitant diseases were vascular disorders (32% overall), musculoskeletal and connective tissue disorders (23% overall), and metabolism and nutrition disorders (18% overall). A similar proportion of subjects in each treatment group had concomitant diseases in the musculoskeletal and connective tissue disorders and the metabolism and nutrition disorders. A higher proportion of subjects in the placebo group compared to the rotigotine treatment groups reported a concomitant disease in the vascular disorders (placebo: 42% subjects, 2.25mg rotigotine: 30% subjects, 4.5mg rotigotine: 32% subjects, 6.75mg rotigotine: 21% subjects). Within the vascular disorders, the most commonly reported disease was hypertension.

Study SP792

The mean age of subjects was 52.3 years; with the majority (84%) of subjects <65 years old. The majority of subjects were female (placebo: 57% subjects, 1.125mg/day rotigotine: 62% subjects, 2.25mg/day rotigotine: 57% subjects, 4.5mg/day rotigotine: 65% subjects, 6.75mg/day rotigotine: 63% subjects), and 94% of subjects were white.

The mean number of years since subjects were diagnosed with RLS was 2.1 years. Overall, 64% of subjects were considered de novo (defined as not having received any RLS medication in the previous 3 years). For subjects who were pre-treated, the mean number of years since the start of RLS drug therapy was 4.1 years. There were no clinically relevant differences across treatment groups with respect to RLS diagnosis information in either the safety set or the full analysis set. The baseline IRLS

sum scores were similar across treatment groups, ranging from 23.1 to 23.6 (severe). The majority of subjects were considered moderately ill and markedly ill based on CGI Item 1 (severity of illness) scores at baseline, with mean scores of 4.6 to 4.7 across all treatment groups. Overall, there were no important differences between treatment groups in the severity of disease at Baseline.

Overall, 87% of the subjects in the safety set had concomitant disease present at screening. The most common concomitant diseases were musculoskeletal and connective tissue disorders (37% overall), nervous system disorders (31% overall), gastrointestinal disorders (27% overall), and immune system disorders (26% overall). The distribution of concomitant diseases was similar across treatment groups. Hypertension was the concomitant disease most often reported (20%) at screening.

Primary endpoints

Table 8: Study results of SP790 and SP792 FAS (with LOCF) of IRLS sum scores at baseline and at end of maintenance period (MP); and mean change from baseline at end of MP.

Study SP790	n	Baseline	End of MP	Mean change	95% CI	p-value
Placebo	114	28.1 ± 6.3	20.0 ± 11.2	-8.0 ± 9.7	-	-
Rotigotine 2.25 mg/day	112	28.1 ± 6.3	14.9 ± 11.1	-13.2 ± 10.0	-5.1 (-2.7;-7.6)	<0.0001
Rotigotine 4.5 mg/day	109	28.2 ± 6.1	12.5 ± 9.6	-15.6 ± 9.5	-7.5 (-5.1;-10.0)	<0.0001
Rotigotine 6.75 mg/day	112	28.0 ± 5.9	11.9 ± 10.9	-16.1± 10.9	-8.2 (-5.7;-10.6)	<0.0001
Study SP792						
Placebo	99	23.5 ± 5.1	14.5 ± 5.1	-9.0 ± 7.7	-	-
Rotigotine 1.125 mg/day	98	23.1 ± 5.0	12.2 ± 8.2	-10.9 ± 8.9	-2.2 (0.2;-4.5)	0.0582
Rotigotine 2.25 mg/day	99	23.2 ± 5.3	12.1 ± 8.7	-11.1 ± 9.3	-3.3 (0.0;-4.6)	0.0535
Rotigotine 4.5 mg/day	95	23.3 ± 4.6	9.9 ± 8.8	-13.4 ± 9.2	-4.5 (-2.2;-6.9)	0.0002
Rotigotine 6.75 mg/day	103	23.6 ± 5.0	9.3 ± 8.5	-14.3 ± 9.4	-5.2 (-2.9;-7.5)	<0.0001

*All values are means ± SD.

Figure 3: Mean IRLS score over time in SP790 (FAS with LOCF)

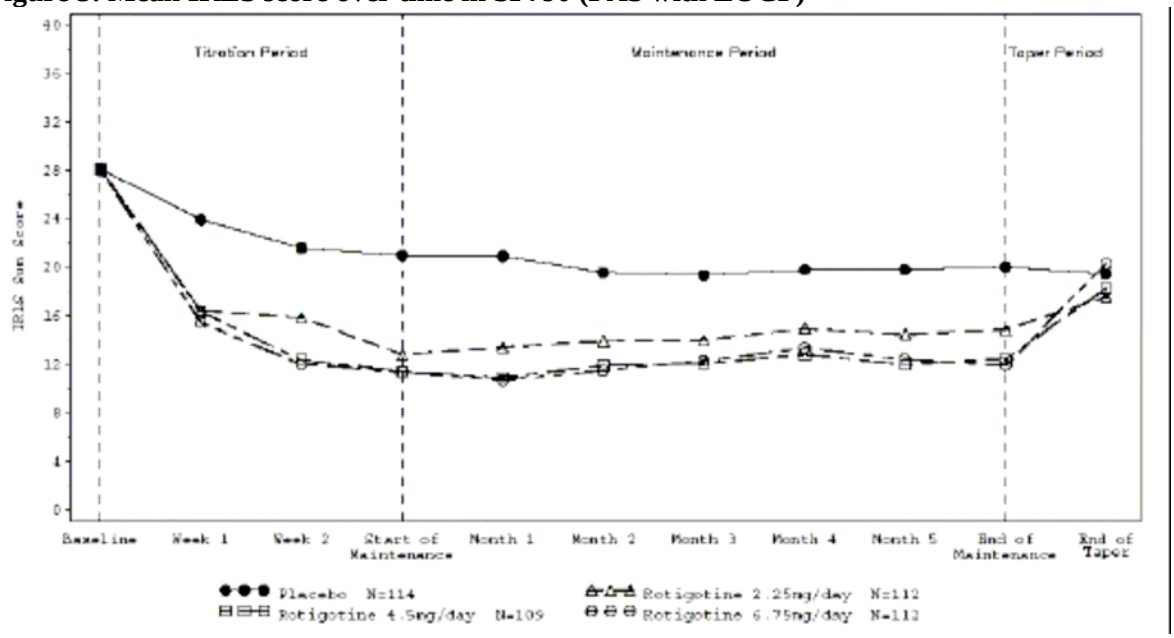


Figure 4: Mean IRLS score over time in SP792 (FAS with LOCF)

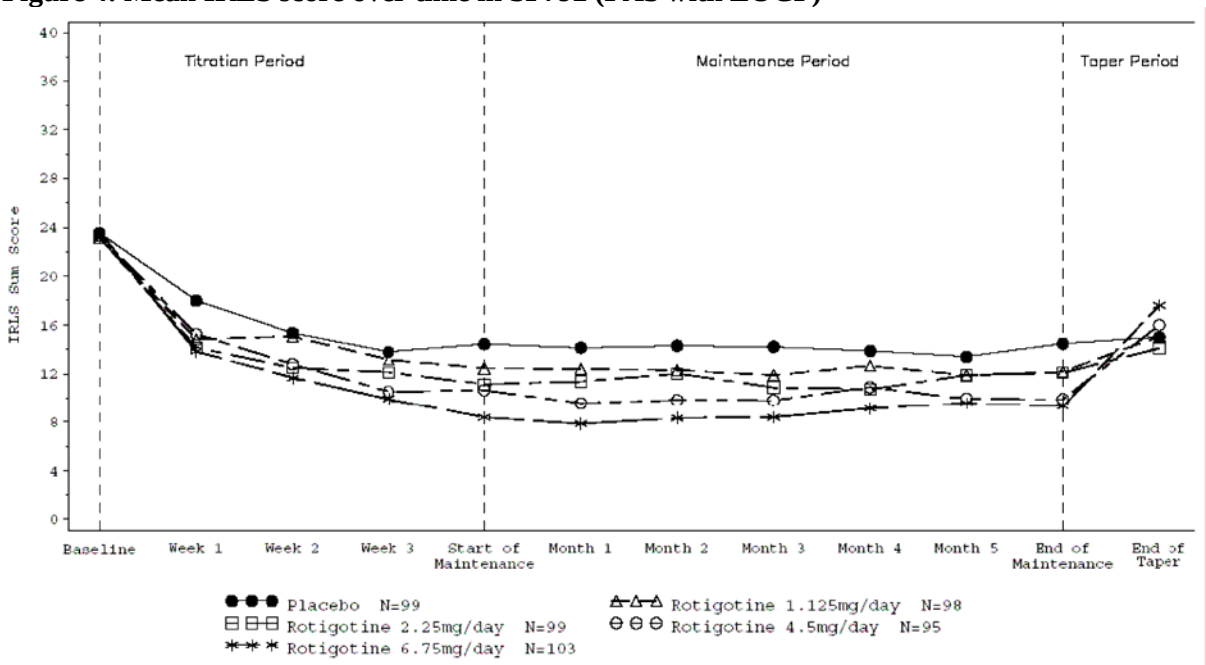


Table 9: Study results of SP790 and SP792 FAS (with LOCF) of GCI Item 1 sum scores at baseline and at end of maintenance period (MP); and mean change from baseline at end MP

Study SP790	**n**	**Baseline**	**End of MP**	**Mean change**	**95% CI**	**p-value**
Placebo	114	5.0 ± 0.8	3.8 ± 1.7	-1.3 ± 1.5	-	-
Rotigotine 2.25 mg/day	112	5.0 ± 0.9	3.0 ± 1.6	-2.0 ± 1.6	-0.76 (-0.38;-1.13)	<0.0001
Rotigotine 4.5 mg/day	109	5.1 ± 0.8	2.7 ± 1.3	-2.4 ± 1.4	-1.07 (-0.69;-1.44)	<0.0001
Rotigotine 6.75 mg/day	112	5.0 ± 0.8	2.6 ± 1.4	-2.5± 1.5	-1.21 (-0.83; -1.58)	<0.0001
Study SP792						
Placebo	99	4.7 ± 0.6	3.3 ± 1.2	-1.4 ± 1.2	-	-
Rotigotine 1.125 mg/day	98	4.7 ± 0.8	2.9 ± 1.3	-1.8 ± 1.5	-0.35 (0.02; -0.72)	0.0503
Rotigotine 2.25 mg/day	99	4.6 ± 0.7	2.9 ± 1.4	-1.7 ± 1.5	-0.32 (0.05; -0.69)	0.0857
Rotigotine 4.5 mg/day	95	4.7 ± 0.8	2.6 ± 1.4	-2.0 ± 1.5	-0.65 (-0.28; -1.02)	0.0007
Rotigotine 6.75 mg/day	103	4.7 ± 0.8	2.4 ± 1.3	-2.4 ± 1.5	-0.90 (-0.54; -1.27)	<0.0001

*All values are means ± SD.

Main secondary endpoints

Table 10 Responder analysis of IRLS score in studies SP790 and SP792 (FAS with LOCF)

Treatment group	**Number of responders (n/N)**		**Treatment difference vs. placebo**	
	SP790	**SP792**	**SP790**	**SP792**
Placebo	29/114 (25%)	37/99 (37%)	-	-
Rotigotine 1.125 mg/day	-	47/98 (48%)	-	10.6
Rotigotine 2.25 mg/day	58/112 (52 %)	51/99 (52%)	26.3	14.1
Rotigotine 4.5 mg/day	63/109 (58%)	57/95 (60%)	32.4	22.6
Rotigotine 6.75 mg/day	62/112 (55%)	69/103 (67%)	29.9	29.6

Table 11 Responder analysis of CGI Item 1 in studies SP790 and SP792 (FAS with LOCF)

Treatment group	Number of responders (n/N)		Treatment difference vs. placebo	
	SP790	**SP792**	**SP790**	**SP792**
Placebo	36/114 (32%)	30/99 (30%)	-	-
Rotigotine 1.125 mg/day	-	40/98 (41%)	-	10.5
Rotigotine 2.25 mg/day	57/112 (51 %)	46/99 (47%)	19.3	16.2
Rotigotine 4.5 mg/day	58/109 (53%)	50/95 (53%)	21.6	22.3
Rotigotine 6.75 mg/day	69/112 (62%)	61/103 (59%)	30.0	28.9

- **Supportive study – SP794**

The objective of study SP794 was to demonstrate that rotigotine is effective in subjects with idiopathic RLS based on the Periodic Limb Movement Index (PLMI = PLMs/total time in bed [TIB]) as measured by polysomnography (PSG). Subjects had to have at baseline an IRLS score ≥15, a CGI Item 1 score ≥4 and have a PLMI if ≥15 based on PSG.

Study design

Phase 3, multicenter, double-blind, randomized, placebo controlled, 2-arm parallel-group trial in subjects with idiopathic RLS.

Subjects were enrolled and randomized to receive placebo or rotigotine in a 2:1 fashion. A run-in period was required for subjects who had previously received RLS therapy or prohibited concomitant medications. Subjects were up-titrated weekly in 2.25mg/day increments to their optimal dose, with a maximum dose of rotigotine 6.75mg/placebo. Dose adjustments were not allowed during the maintenance period.

Sleep lab measurements were performed in the 2 consecutive nights prior to baseline and prior to the end of maintenance. Primary endpoint was the reduction of the PLMI at the end of the maintenance period compared to baseline. Secondary endpoints were: PLMSAI (Periodic Limb Movements during Sleep Arousal Index; PLMs during sleep with arousals/total sleep time), sleep efficiency [%; sleep time/total time in bed (TIB)], IRLS sum score, CGI Item 1 (severity of illness), and Medical Outcome Study (MOS) Sleep Scale-Adequacy Subscale.

Results

Table 12: ANCOVA analysis of PLMI at baseline and at the end of the maintenance period (FAS)

Treatment	N	Geometric mean at Baseline	LS mean	Treatment ratio	p-value
Placebo	20	37.4	32.69	-	-
Rotigotine	41	50.9	7.7	4.25	<0.0001

At the end of the maintenance period, rotigotine-treated subjects had 16% of their baseline PLMI value present while placebo-treated subjects had 73% of their baseline PLMI values present. Results in the Per Protocol Set (PPS) were consistent with the results of the primary analysis.
26% of the rotigotine treated subjects had a IRLS score of 0 at the end of the maintenance period, reflecting that they did not have symptoms of RLS. None of the patients in the placebo group had a score of 0 at the end of the maintenance period.

Clinical safety

A total of 1432 subjects with RLS (1309 subjects treated with rotigotine) were included in the safety analysis. All subjects receiving at least one dose of trial medication (rotigotine or placebo) were included in the safety analyses.

Patient exposure

Rotigotine exposure exceeded 6 months for most subjects: 6 to 12 months (23%), 1 to 2 years (31%), and >2 years (15%). The maximum duration of exposure was 1327 days (~3.5 years). The maximum dose of longest duration was 4 mg/24h. The majority of subjects were exposed to mean rotigotine doses ranging from 1 to <2 (41%) or 2 to <3 mg/24h (32%) followed by 0.5 to <1 (18%) and 3 to <4 mg/24h (10%). For most subjects the dose of longest duration was either rotigotine 2 (29%), 1 (25%), or 3 mg/24h (23%).

Adverse events

In a pooled analysis of studies SP790 and SP792, 68% of placebo-treated subjects and 83% of all rotigotine-treated subjects with RLS had at least one adverse event.

The adverse events with the highest incidence in rotigotine-treated subjects was application and instillation site reactions (34%), nausea (19%), headache (17%), and asthenic conditions (11%). In rotigotine-treated subjects, all occurrences of application and instillation site reactions and most occurrences of nausea, asthenic conditions, somnolence, and dizziness were regarded as related to trial medication by the investigators. Most adverse events were mild or moderate in intensity and dose related.

Application and instillation site reaction occurred in 34% in rotigotine treated subjects compared to 4% in placebo. Among all rotigotine-treated subjects, the incidence of nausea was notably higher during the titration period compared with the maintenance period. This effect was observed across all doses of rotigotine.

In contrast, the incidence of application and instillation site reactions was lower during the titration period compared with the maintenance period. In all rotigotine-treated subjects, median time to first onset of nausea was 8 days, and median time to first onset of application and instillation site reaction was 58 days.

Serious adverse events and deaths

A total of 20/1309 (1.5%) rotigotine-treated subjects had at least one SAE assessed by the investigator as drug related. The most frequent drug-related SAEs were application and instillation site reaction (n=6, <1%), nausea (n=2, <1%), syncope (n=2, <1%), and sleep attacks (n=2, <1%). No other specific drug-related SAE was observed in >1 subject.

Table 13: All drug-related serious adverse events occurring in rotigotine-treated subjects

MedDRA SOC/ HLT[b] or PT	Total Rotigotine N=1309 n (%)
At least 1 drug-related SAE	20 (1.5)
Cardiac Disorders	
Sinus bradycardia	1 (<0.1)
Ear and labyrinth disorders	
Tinnitus	1 (<0.1)
Gastrointestinal disorders	
Nausea	2 (0.2)
General disorders and administration site conditions	
Application and instillation site reactions[a]	6 (0.5)
Application site reaction	6 (0.5)
No therapeutic response	1 (<0.1)
Injury, poisoning and procedural complications	
Fall	1 (<0.1)
Investigations	
Electrocardiogram change	1 (<0.1)
Hepatic enzyme increased	1 (<0.1)
Nervous system disorders	
Syncope	2 (0.2)
Balance disorder	1 (<0.1)
Somnolence	1 (<0.1)
Memory impairment	1 (<0.1)
Dizziness	1 (<0.1)
Dysarthria	1 (<0.1)
Psychiatric disorders	
Sleep attacks	2 (0.2)
Confusional state	1 (<0.1)
Vascular disorders	
Deep vein thrombosis	1 (<0.1)

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class

There was one death among subjects participating in the RLS program. The patient suffered from a aortic disorder followed by ventricular hypertrophy leading to aortic valve replacement. The investigator assessed the aortic disorder as unlikely related and the remaining events as not related to the rotigotine medication.

Laboratory findings

Small increases in liver function parameters and blood urea nitrogen (BUN) were observed in subjects treated with rotigotine compared to subjects treated with placebo.

The only chemistry-related adverse event reported by ≥1% of subjects in the total rotigotine group was hypercholesterolemia (1%).

Discontinuation due to AES

Six percent of placebo-treated subjects and 18% of all rotigotine-treated subjects with RLS had a adverse event that led to discontinuation of trial medication. Among rotigotine-treated subjects, the overall incidence of discontinuation of trial medication due to a adverse event was 9%, 16%, 18%, and 25% in the 0.5 mg/24h, 1 mg/24h, 2 mg/24h, and 3 mg/24h randomized dose groups, respectively.

4. Pharmacovigilance

The MAH submitted a revised Risk Management Plan (see Table 14).

Table 14

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Identified risks		
Application site reactions	- routine pharmacovigilance - postapproval safety study under conditions of routine clinical practice (long-term patient registry) - additional information from ongoing clinical trials	- Warning in section 4.4 of the SPC (Specific recommendations about how to reduce and manage application site reactions are provided). - Method of administration in section 4.2 of the SPC provides important information - Listed under Section 4.8
Sleep attacks / sudden onset of sleep	- routine pharmacovigilance - postapproval safety study under conditions of routine clinical practice (long-term patient registry). Particular attention will be paid to sleep attacks (defined as events of special interest per protocol. - additional information from ongoing clinical trials	- Warning in section 4.4 of the SPC (Sleep attacks have been associated with Neupro; prescribers should continually reassess; dose reduction or termination may be considered). - Warning in section 4.7 of the SPC (Patients informed not to drive or engage in other activities which may place them at risk.) - Listed under section 4.8.
Postural/orthostatic hypotension	- routine pharmacovigilance - postapproval safety study under conditions of routine clinical practice (long-term patient registry) - additional information from ongoing clinical trials	- Warning in section 4.4 of the SPC (Dopamine agonists are associated with postural/orthostatic hypotension; recommended to monitor blood pressure.) - Listed under section 4.8
Impulse control and compulsive disorder	- routine pharmacovigilance - postapproval safety study under conditions of routine clinical practice (long-term patient registry) - additional information from ongoing clinical trials	- Warning in section 4.4 of the SPC (Pathologic gambling, increased libido and hypersexuality reported with dopamine agonists and Neupro.) - Listed under section 4.8.
Potential risks		
Cardiovascular fibrosis	- Routine pharmacovigilance - Postapproval safety study under conditions of routine clinical practice (long-term patient registry). Particular attention will be paid to cardiac valve fibrosis-related signs and symptoms	- Warning in section 4.4 of the SPC (fibrotic complications associated with ergot-derived dopaminergic agents; whether associated with non-ergot derived dopamine agonists is unknown.)

	(defined as events of special interest per protocol). - Additional information from ongoing clinical trials - Independent, prospective, multicenter trial on cardiac fibrosis in Parkinson's disease patients on dopamine agonists	
Effect on retina	- routine pharmacovigilance - postapproval safety study under conditions of routine clinical practice (long-term patient registry) - additional information from ongoing clinical trials	- Warning in section 4.4 of the SPC for Neupro (regular ophthalmologic monitoring is recommended.)
Neuroleptic malignant syndrome after abrupt withdrawal	- routine pharmacovigilance - postapproval safety study under conditions of routine clinical practice (long-term patient registry) - additional information from ongoing clinical trials	- Warning in section 4.4 of the SPC (although not reported with Neupro, neuroleptic malignant syndrome has been reported with abrupt withdrawal of dopaminergic therapy; recommended to taper treatment.)
Augmentation in RLS	- Routine pharmacovigilance - Additional information from ongoing clinical trials	- Warning in Section 4.4 of the SPC for RLS (Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in severity of symptoms, and spread of symptoms to involve other body parts.)
Rebound in RLS	- Routine pharmacovigilance - Additional information from ongoing clinical trials	- Warning in section 4.2 of the SPC for RLS. (Neupro should be discontinued gradually. Following this procedure rebound was not observed.)
Missing information		
Patients with severe hepatic impairment	- Routine pharmacovigilance	- Warning in Section 4.2 of the SPC (Caution is advised when treating patients with severe hepatic impairment, which may result in lower rotigotine clearance. Neupro has not been investigated in this patient group. A dose reduction might be needed in case of worsening of the hepatic impairment).

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5. Overall conclusions and benefit-risk assessment

The clinical efficacy of rotigotine for the treatment of moderate to severe RLS was assessed in two pivotal studies (SP790 and SP792). The rotigotine doses used in these studies correspond to the proposed doses (from 1 to 3 mg/24h) in the SPC. The IRLS scale and the CGI type 1 score were used as clinical efficacy endpoints. Both scales are internationally recognised to study treatment effects in patients with RLS. Both studies demonstrated a comparable clinically significant improvement of RLS on the IRLS and the CGI Item 1 score. The responder analysis confirmed the clinical relevance of the effect. Moreover, the effect is maintained over a six months period (see figures 3 and 4).

In terms of safety, no new concerns emerged in the RLS population in comparison to the safety profile of rotigotine in PD population. The maximum dose for the treatment of PD is much higher (16mg/24h) than for the treatment of RLS (3 mg/24h).

Application site reactions, nausea, asthenia, headache and somnolence were reported in higher frequencies with rotigotine than with placebo. Since RLS patients are possibly more active and surely less bradykinetic than PD patients, somnolence and asthenia can be of concern for this population. Satisfactory responses were provided by the MAH to these concerns and information in the SPC/PL has been reflected, as appropriate.

Although an absence of augmentation and rebound following discontinuation was shown with the available short term data, these effects cannot be ruled out with the use of dopamine agonists. The CHMP therefore requested a plan to study augmentation and rebound more extensively, to which the MAH committed to.

In conclusion, the CHMP considered that the benefit risk assessment of Neupro in the proposed indication '*symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in adults.'* is positive and recommended the variation to the Marketing Authorisation.

6. Conclusions

On 24 April 2008, the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.