European Medicines Agency

London, 09 January 2007
EMEA/CHMP/38174/2007
Product name: **Neupro**
Procedure No. **EMEA/H/C/000626/II/0003**

SCIENTIFIC DISCUSSION

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1.1. Introduction

Neupro (rotigotine) is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease.

Parkinson's disease (PD) is a neurodegenerative disorder characterized by a progressive loss of dopaminergic neurons in the substantia nigra. Parkinson's disease is clinically characterised by bradykinesia, resting tremor, rigidity and postural reflex impairment. The cause of Parkinson's disease is, at present time, unknown. Parkinson's disease is a slowly progressive disease. Pharmacological intervention of Parkinson's disease is symptomatic. Improvement of an impaired dopaminergic neurotransmission is the backbone of therapy. About 70% of patients with PD will require symptomatic therapy within 2 years of disease onset. The choice between levodopa+decarboxylase inhibitor or a dopamine-agonist for initial therapy remains controversial. On the one hand levodopa+decarboxylase inhibitor is more effective and better tolerated than dopamine-agonists, on the other hand there are concerns that it might be toxic to dopaminergic neurons and that it promotes the development of motor fluctuations and dyskinesia.

Rotigotine (Neupro) belongs to the group of non-ergolinic dopamine agonists and shows a close structural analogy to dopamine and apomorphine. 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.

The variation refers to an extension of the therapeutic indication to include *'the treatment of the signs and symptoms of advanced idiopathic Parkinson's disease 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).'*

Consequential changes were made to relevant sections of the Summary Product Characteristics (SPC). The Package Leaflet (PL) was updated accordingly. In addition, contact details of Bulgaria and Romania local representatives were also included.

1.2. Non clinical aspects

The pharmacokinetic and toxicological results from animal studies, supportive of the approved formulations have been previously assessed at the time of the initial application for Neupro. The dose of 18 mg (40 cm^2 patch size, i.e 8 mg/24h), maximum therapeutic dose observed for the currently approved indication, was used as basis to calculate the safety margins of rotigotine.

This variation application concerns an extension of indication to include the treatment of signs and symptoms of advanced stage Parkinson patients in combination with levodopa. The proposed maximum therapeutic dose is 36 mg (i.e 16 mg/24h) and has been used in the pivotal clinical study SP515, conducted in patients with advanced Parkinson's disease.
Within this variation application, the MAH has therefore proposed to update the calculation of the safety margins and revise the product information accordingly.

The toxicological safety margins were calculated for the maximum human dose of 36 mg for the treatment of advanced stage of Parkinson's disease based on the mean maximum plasma levels in patients , achieved during the maintenance phase (i.e. 6.71 ng/mL).

Safety ratios at No-Observed-Effect Levels (NOELs)

Table 1: Safety ratios at NOELs

Maximum therapeutic dose:	36 mg (80 cm^2) / 24 hour	**C_{max}*:** 6.71 ng/mL
Repeat dose toxicity studies	**NOEL (mg/kg)**	**Safety ratio C_{max}***
Rat, 6 months	0.5	0.3
Monkey, 12 months	1	0.4
Reproductive and developmental studies		
Mouse, Segment II	30 foetus	10
Rat, Segment I	>15 male	>8
Rat, Segment I	1.5 female	0.6
Rat, Segment II, teratogenicity	1.5 foetus	0.6
Rabbit, Segment II	25 foetus	74

*AUC (daily) is not available; therefore calculation has not been made

At doses above the NOEL, the most prominent systemic effects, such as restlessness and 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.

Safety ratios at Well Tolerated Dose Levels (WTDLs)

Well tolerated dose levels (WTDLs) were defined by the MAH as to show: no substance-related deaths; no findings which are not related to the pharmacodynamic properties of rotigotine; no irreversible rotigotine-related effects.

Table 2: Safety ratios at Well Tolerated Dose Levels (WTDLs) based on plasma levels

Maximum therapeutic dose	**Dose**	**Cmax**
	36 mg (80 cm^2) / 24 hour	6.71 ng/mL
Study	**WTDL (mg/kg)**	**Safety ratio Cmax**
Mouse, 3 months, s.c.	30	5
Rat, 3 months, s.c.	3	1
Rat, 6 months, s.c.	2.5	1
Rat, 28 days, i.v.	8	No data on plasma levels available
Monkey, 12 months, s.c.	10	7
Monkey, 28 days, i.v	8	No data on plasma levels available

Table 3: Safety ratios at Well Tolerated Dose Levels (WTDLs) based on doses

Maximum therapeutic dose:		36 mg (80 cm^2) = 0.4 mg/kg*	= 14.8 mg/m^2**
Study	**WTLD (mg/kg)**	**Safety ratio based on mg/kg***	**Safety ratio based on body surface area****
Mouse, 3 months, s.c.	30	75	6.1
Rat, 3 months, s.c.	3	7.5	1.2
Rat, 6 months, s.c.	2.5	6.25	1
Rat, 28 days, i.v.	8	20	3.2
Monkey, 12 months, s.c.	10	25	8.1
Monkey, 28 days, i.v	8	20	6.5

*a mean body weight of 65 kg for humans was applied

** calculated according to US FDA guidance for industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers

Given the results provided by the long-term pivotal repeat-dose toxicity studies, which were mainly related to pharmacodynamic, dopamine agonistic related-effects, the use of the WTDL is interesting and may reflect a more realistic estimation of the safety margins.

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 advanced Parkinsonian patients (36 mg) were acceptable.

1.3. Clinical aspects

The clinical development program to support the extension of indication of Neupro to advanced-stage Parkinson's disease included 3 placebo-controlled studies:

- 1 phase II study (SP511) was conducted in patients with advanced stage Parkinson's disease and evaluated dose-response with the following patches: 9 mg/20 cm^2, 18mg /40 cm^2 and 27mg /60 cm^2.

- 2 pivotal phase III studies (SP650 and SP515) , were conducted in patients with advanced-stage Parkinson's disease. Both clinical studies were multicenter, randomised, double-blind and parallel group design, consisting of a titration period in which the patients were titrated to their optimal dose or up to a maximum dose, followed by a maintenance and de-escalation periods. In study SP515, treatment arm included pramixepole, as an active control and the patients were receiving doses up to 36 mg (i.e 16 mg/24h).

Additional phase II/IIIb open-label studies were conducted and mainly evaluated the safety and tolerability of rotigotine in patients with advanced stage Parkinson's disease. Particularly, two phase IIIb studies were performed, respectively, to evaluate the effect of overnight switching from ropinirole, pramipexole, or cabergoline to rotigotine (SP824) and the effect of rotigotine on early morning motor impairment and sleep disorders (SP826).

Clinical Efficacy

- Dose-Response Study

Study SP511

METHODS

Primary objective

The primary objective of this phase II study was to determine the dose group of rotigotine patch that shows efficacy with optimal benefit/risk ratio in subjects with advanced-stage, idiopathic Parkinson's disease.

Design

SP511 was randomised, double-blind, placebo controlled parallel study with 4 arms respectively placebo, rotigotine at 9mg (20 cm^2), 18 mg (40cm^2) and 27mg (60cm^2).

Study Participants

Subjects with idiopathic Parkinson's disease who were required to exhibit the cardinal sign of bradykinesia and at least 1 of the additional signs of advanced-stage disease: resting tremor, rigidity, and/or impairment of postural reflexes. Furthermore, these subjects were not adequately controlled on the levodopa dose (in combination with benserazide or carbidopa), which was judged by the treating

physician to be optimal. At Baseline, subjects had motor fluctuations with diary confirmation that at least 2.5 hours/day were spent in the 'off' state. Subjects with unpredictable 'on'/'off' fluctuations were excluded from the trial.

Treatment study arms

In study SP511, the target doses selected in patients with advanced-stage Parkinson's disease were 9.0mg (20cm^2), 18.0mg (40cm^2), and 27mg(60cm^2) rotigotine. The subjects were titrated to their target doses in weekly increments of 4.5mg (10cm^2), starting at 9.0mg/day (20cm^2).
Back-titration could be performed once during the entire titration period. Once a back titration was performed, the patient was maintained at the back titrated dose for the remainder of the study period. If another dose reduction was necessary, the subject was withdrawn from the study. Different combinations of 4 patches (including placebo, 4.5mg, and 9.0mg patches) were used to titrate subjects weekly for 5 weeks to their target doses. Patients randomised to 9mg (20cm^2) and 18.mg (40cm^2) received placebo patches for 4 and 2 weeks, respectively. Patients in each treatment group were maintained on the target dose for 7 weeks. The maximum treatment exposure to rotigotine was 3 months.

Primary endpoint

The primary variable was the absolute change from baseline to end of treatment in absolute time spent 'off'.

RESULTS

A total of 324 subjects were randomised to treatment: 84 to placebo and 240 to rotigotine (of which 2 discontinued the trial prior to receiving randomised medication). Of the 238 remaining subjects randomised to rotigotine, 15 never received rotigotine because of sham back titrations.
The different treatment groups were well balanced with respect to age, sex, body weight, ethnic origin, and duration of disease (range of 7.3 to 7.9 years). At baseline, the absolute time spent "off" was similar across treatment groups (range 5.97 – 6.47 hours). The baseline UPDRS (Unified Parkinson's Disease Rating Scale) scores (I, II, and III) were well balanced between treatment groups. In addition, subject's distribution using Hoehn & Yahr staging, levodopa use at baseline, and agreement for training of subjects for completion of subject's diaries were well balanced between treatment groups.

Table 4

Summary of absolute change from Baseline to end of Treatment in absolute time spent "off" in SP511 (FAS)

Visit	Statistic	Placebo N=81	9.0mg Rotigotine N=77	18.0mg Rotigotine N=75	27.0mg Rotigotine N=77
Baseline (Visit 2)	Mean±SD, h	6.32±2.477	5.97±2.541	6.47±2.632	6.04±2.854
EOT (Visit 9)	Mean±SD, h	4.48±3.439	3.96±3.166	4.68±3.434	3.68±3.539
	Mean±SD change from Baseline, h	-1.83±3.134	-2.00±3.337	-1.79±2.943	-2.35±3.409
	Adjusted mean (SED)	-1.81 (0.34)	-2.13 (0.35)	-1.72 (0.36)	-2.44 (0.35)
	Net effect[b] (SED)	-	-0.32 (0.48)	0.09 (0.49)	-0.63 (0.48)
	95% CI	-	-1.266, 0.632	-0.867, 1.049	-1.580, 0.320
	p-value[a]	-	-	-	0.0965

ANCOVA=Analysis of Covariance, CI=confidence interval, EOT=end of Treatment, FAS=Full Analysis Set, SD=standard deviation, SED=standard error of the difference

a. P-value based on ANCOVA; model included treatment group as a factor, country as a stratification factor, and Baseline value as a covariate.

b. Treatment-adjusted mean minus placebo-adjusted mean.

Table 5

Summary of >30% responder rates for relative change in absolute time spent "off" at the end of Treatment in SP511 (FAS)

	Placebo N=81	9.0mg Rotigotine N=77	18.0mg Rotigotine N=75	27.0mg Rotigotine N=77
Responder, n (%)	41 (51)	40 (52)	33 (44)	50 (65)
p-value[a]	-	0.8750	0.4268	0.0780
Odds ratio[b]	-	1.056	0.763	1.806
95% CI[b]	-	0.563, 1.982	0.403, 1.445	0.947, 3.443

CI=confidence interval, FAS=Full Analysis Set

a. P-value from 2-sided Fisher's Exact Test on treatment versus placebo.

b. Odds ratio and 95% CI obtained from parameter estimates for treatment from the logistic regression model including treatment as a factor and country as a stratification factor. Odds ratio >1 indicates that the chance of being a responder are higher for the active treatment group than for the placebo group.

Data source: SP511 Table 20.9.2.1

Results from study SP511 showed consistent improvement after application of rotigotine 27mg (60 cm2) patch.

- Main studies

Studies SP650 and SP515

METHODS

Objectives

The objectives of the 2 phase III studies (SP650 and SP515) were to evaluate efficacy, safety and tolerability of rotigotine transdermal patch as adjuvant to levodopa in advanced idiopathic Parkinson's disease as compared to placebo and active control i.e. pramipexole (only SP515).

Study Design

Studies SP650 and SP515 had a randomised, double-blind, placebo controlled parallel study design.

Study Participants

Subjects with advanced idiopathic Parkinson's Disease, who experienced wearing-off type motor fluctuations on levodopa.

Subjects were included if they had been diagnosed with idiopathic Parkinson's disease of >3 years in duration, had a Hoehn & Yahr stage II through IV as observed in both the 'on' and 'off' state, were on a stable dose of levodopa of at least 200 mg/day (SP650) or 300 mg/day (SP515) for at least 28 days prior to baseline, were not adequately controlled on anti-Parkinson medication as judged by the treating investigator to be optimal, had an average of 2.5 hours/day or more spent in the 'off' state at screening; were on a stable dose of all anti-Parkinsonian medications at least 28 days prior to baseline. For the duration of the trial the concurrent anti-Parkinson medication allowed, had to remain stable.

Main exclusion criteria were patients with a history of surgical interventions for Parkinson's disease, serious concurrent co-morbidity, QTc interval abnormalities, orthostatic hypotension and history of skin sensitivity to adhesives.

Treatment study arms

Procedure

The run-in period was approximately 28 days. The subsequent dose escalation phase was 5 weeks (SP650) or 7 weeks (SP515).
In study SP650, patients were titrated up to the target dose (18 or 27 mg/day) or maximum tolerated doses.
In study SP515, patients were titrated up to the optimal dose, tolerated dose or maximum dose (36mg/day).
The maintenance phase lasted 24 weeks (SP650) or 16 weeks (SP515). In the maintenance phase, patients remained on the optimal doses determined. During the first 2 weeks of the maintenance phase L-dopa could be reduced. At the end of the maintenance phase a blinded de-escalation over 8 days (SP650) or 6 days (SP515) days followed.

Doses

In study SP650, subjects were randomised to rotigotine transdermal patch 18 mg/day, 27 mg/day or placebo. All patients received two 10 cm^2 patches (placebo patch or 4.5 mg rotigotine) and two 20 cm^2 patches (placebo or 9.0 mg rotigotine).
Based on the targeted daily dose, the titration schedule is presented in the following table:

Table 6

Daily dose of rotigotine or placebo during the dose titration phase

Week of Escalation	Treatment Group					
	Rotigotine target dose 18.0mg/day		Rotigotine target dose 27.0mg/day		Placebo	
	Rotigotine Patches	Placebo Patches	Rotigotine Patches	Placebo Patches	Rotigotine Patches	Placebo Patches
Week 1	1×20cm^2	2×10cm^2 1×20cm^2	1×20cm^2	2×10cm^2 1×20cm^2	-	2×10cm^2 2×20cm^2
Week 2	1×10cm^2 1×20cm^2	1×10cm^2 1×20cm^2	1×10cm^2 1×20cm^2	1×10cm^2 1×20cm^2	-	2×10cm^2 2×20cm^2
Week 3	2×20cm^2	2×10cm^2	2×20cm^2	2×10cm^2	-	2×10cm^2 2×20cm^2
Week 4	2×20cm^2	2×10cm^2	1×10cm^2 2×20cm^2	1×10cm^2	-	2×10cm^2 2×20cm^2
Week 5	2×20cm^2	2×10cm^2	2×10cm^2 2×20cm^2	-	-	2×10cm^2 2×20cm^2

In study SP515 subjects were randomised to rotigotine transdermal patch, pramipexole capsules or placebo.
The titration schedule for active treatment or corresponding placebo patches/capsules is presented in the following table:

Table 7. Contents of weekly titration kits during dose escalation per treatment group

Week of Titration	Treatment Group					
	Rotigotine		Pramipexole		Placebo	
	Rotigotine patches (od)	Placebo capsules (tid)	Placebo patches (od)	Pramipexole dihydro-chloride capsules (tid)	Placebo patches (od)	Placebo capsules (tid)
Week 1	1 x 20cm^2	1 x 0.125mg	1 x 20cm^2	1 x 0.125mg	1 x 20cm^2	1 x 0.125mg
Week 2	1 x 30cm^2	1 x 0.25mg	1 x 30cm^2	1 x 0.25 mg	1 x 30cm^2	1 x 0.25mg
Week 3	2 x 20cm^2	1 x 0.5mg	2 x 20cm^2	1 x 0.5 mg	2 x 20cm^2	1 x 0.5mg
Week 4	1 x 30cm^2 + 1 x 20cm^2	1 x 0.5mg + 1 x 0.25mg	1 x 30cm^2 + 1 x 20cm^2	1 x 0.5mg + 1 x 0.25mg	1 x 30cm + 1 x 20cm^2	1 x 0.5mg + 1 x 0.25mg
Week 5	2 x 30cm^2	2 x 0.5mg	2 x 30cm^2	2 x 0.5mg	2 x 30cm^2	2 x 0.5mg
Week 6	2 x 20cm^2 + 1 x 30cm^2	1 x 0.25mg + 2 x 0.5mg	2 x 20cm^2 + 1 x 30cm^2	1 x 0.25mg + 2 x 0.5mg	2 x 20cm^2 + 1 x 30cm^2	1 x 0.25mg + 2 x 0.5mg
Week 7	2 x 30cm^2 + 1 x 20cm^2	3 x 0.5mg	2 x 30cm^2 + 1 x 20cm	3 x 0.5mg	2 x 30cm^2 + 1 x 20cm	3 x 0.5mg

od=once daily, tid=3 times daily

Concomitant treatment

Subjects had to be on a stable dose of levodopa defined as no change in total daily dose and in the treatment regimen for at least 28 days prior to baseline. Subjects were not permitted to adjust their daily dose of L-DOPA at any time during the course of the trial. In case of adverse events due to excessive dopaminergic stimulation, the physician could reduce the L-DOPA dose but only in the first 2 weeks of the maintenance phase. Thereafter the dose had to remain stable.

Concurrent medication acting on the dopaminergic system other than levodopa was not allowed. Other anti-Parkinson's drugs and/or CNS active drugs were allowed, provided the dose was stable and kept stable during the trial. In study SP650, COMT-inhibitors were not allowed whereas in study SP515 entacapone was allowed.

Efficacy endpoints

Subjects recorded the time spent 'off', 'on without troublesome dyskinesias', 'on with troublesome dyskinesias", sleep, and time of anti-Parkinson medication. Before study entry, subjects were intensively trained to recognise these motor stages and how to complete their diaries. Three diaries had to be completed for 3 consecutive days prior to the next visit. A diary was considered valid if at least 22 of the 24 hours data were completed. Less than 2 valid diaries out of 3 was considered missing.

According to different regulatory recommendations, the primary endpoint was defined differently in Europe (EU) and the United States (US).
In the EU, the primary efficacy parameter was the proportion of responder at the end of treatment. A responder was defined as a subject with a ≥ 30% decrease in absolute time spent 'off'. In the US, the primary efficacy parameter was the absolute reduction in absolute time spent 'off' at the end of treatment.

Secondary outcomes variables notably included on/off time based variables, absolute change in on stage of UPDRS II (ADL), UPDRS III (Motor score) and UPDRS IV (impairment), Parkinson's Disease Questionnaire (SP515 only), EuroQoL (SP650 only) and clinical global impression.

Sample size

Study SP560
Assuming the true proportions of responders is 60% and 40% for active treatment and placebo respectively, a sample size of 110 subjects in each treatment arm was needed to detect such difference, (α=0.05, 1-β=0.80).

Study SP515
The sample size was determined by the active comparison of rotigotine to pramipexole.

Assuming a true responders rate of 50% for both active treatment arms, 180 subjects per active arm was needed to ensure that the lower bound of the two sided $CI_{95\%}$ does not exceed the non-inferiority margin of 15% (1-β=0.80).

For the absolute reduction in absolute time spent 'off' at the end of treatment, sample size was calculated on the analysis as performed for the EU. For the comparison to placebo, the expected 20% difference as given in the responder endpoint corresponded to 1.5 hours reduction in absolute 'off' time (power > 0.95, SD 2.48). For the active comparison the 15% non-inferiority margin corresponded to a reduction in absolute 'off' time of approximately 1.2 hours (power > 0.95).

Assuming a difference in responder's rate with placebo of 20%, 90 subjects are needed in the placebo arm to establish a statistical significant difference, if it exists (2-sided normal approximation test, α=0.05, 1-β=0.85, 2:2:1 randomization ratio).

Statistical methods

No interim analyses or data monitoring board meetings were conducted.

The responder status was analyzed using large sample normal approximation. The analysis of absolute change in 'off' time was evaluated by means of an ANCOVA (analysis of covariance) model with treatment as main effect and geographic region and baseline absolute time spent 'off' as covariates.
The primary analysis concerned the Full Analysis Set (FAS). The Full Analysis Set incorporates all randomized patients receiving trial medication and with a valid baseline visit (4 valid diary cards out of 6) and at least 1 valid post-baseline visit (2 valid diary cards out of 3). For non-inferiority testing (SP650) the FAS data set was also the primary analyses set.

In study SP650, the first comparison was between rotigotine 27 mg/day and placebo (α=0.025 1-sided) for superiority of rotigotine responder rate to the placebo responder rate. If significant, the second comparison was between rotigotine 18 mg/day versus placebo (α=0.025 1-sided).
In study SP515, the first comparison was between placebo and rotigotine (α=0.05 2-sided) for superiority of rotigotine responder rate to the placebo responder rate. If significant, the second comparison was between rotigotine and pramipexole for non-inferiority (α=0.025 1-sided), if non-inferior and the corresponding confidence interval (CI) lied above 0, then a 2-sided p-value for superiority of rotigotine to pramipexole was to be calculated.

Secondary variables were presented using descriptive statistics only.

Missing values

Only data from valid visits were used for analyses. A daily diary card was regarded to be valid if at least 22 hours of the 24 hour clock were filled in. The missing hours were imputed according to the proportions 'on/off' of the observed hours. Further, a visit was regarded only valid if for the baseline

visit at least 4 diary cards out of the 6 were valid and for the post-baseline visits at least 2 diary cards out of 3 were valid. For missing data the last observation carried forward was used.

RESULTS

Recruitment / Participant flow / Numbers analysed

Table 8. Number of patients recruited, randomised and completing

STUDIES	**SP650**			**SP515**		
$n_{recruited}$	462			604		
	Placebo	Rotigotine 18 mg/day	Rotigotine 27 mg/day	Placebo	Rotigotine	Pramipexole
$n_{randomised}$	120	120	111	101	204	201
$n_{non\text{-}completers}$	23%	28%	27%	26%	11%	15%
Lack of efficacy	9.2%	5.8%	4.5%	6.9%	1.5%	1.5%
Adverse events	9.2%	15.0%	15.3%	5.9%	5.4%	7.0%
%% of n-randomised						
In safety data set (SS)	100%	98%	100%	100%	100%	100%
In full analyses set (FAS)	99%	94%	98%	99%	99%	100%
In per protocol set (PPS)	71%	70%	70%	72%	87%	82%
Completers data set (CS)	n.a			73%	88%	84%
PK data set				30%	29%	27%

The safety data set (SS) included all subjects randomized who have received at least one dose of trial medication.
The full analyses data set (FAS) included all randomized subjects who received treatment and having a baseline and at least one post-baseline measurement for the primary variable.
The per protocol data set (PPS) was a subset of the full analysis set by excluding all subjects with less than 8 weeks of exposure to the trial medication in the maintenance phase or the subjects with a major protocol deviation.
The completer data set (CS) was a subset of the full analysis excluding all subjects without valid end of maintenance visit.
n.a: not applicable

Baseline data

The baseline data (e.g. patient and disease characteristics, use of L-dopa and history of previous anti-Parkinson medication) were equally distributed over the treatment arms. Especially the UPDRS scores at baseline indicates equal disease burden.

A summary of the baseline data for studies SP650 and SP515 is presented in the following table.

Table 9. **Patient and Disease characteristics at baseline**

	SP650			SP515		
	Placebo	Rotigotine 18 mg/day	Rotigotine 27 mg/day	Placebo	Rotigotine	Pramipexole
n_{ss}	120	118	111	99	205	202
Patient characteristics						
Age (X, SD)	66.3 (9.7)	66.5 (10.0)	64.5 (10.4)	64.7 (10.1)	64.3 (8.9)	63.3 (9.7)
< 65 years	36.7%	39.8%	50.5%	45.5%	45.9%	48.5%
65-74 years	45.0%	35.6%	31.5%	38.4%	43.9%	56.9%
% > 75 years	20.0%	24.6%	18.0%	16.2%	9.4%	9.4%
Disease characteristics						
Duration PD (x,sd) (years)	7.7 (4.0)	7.7 (4.3)	7.8 (4.6)	8.3 (4.9)	8.8 (4.4)	8.4 (4.7)
Hoehn-Yahr Stage						
Stage 1	0.0%	0.8%	2.7%	0.0%	0.5%	0.0%
Stage 2	61.7%	60.2%	56.8%	18.2%	19.5%	18.8%
Stage 3	34.1%	31.3%	35.1%	51.5%	57.6%	58.4%
Stage 4	4.2%	5.1%	5.4%	30.3%	22.0%	22.3%
Stage 5	0.0%	0.0%	0.0%	0.0%	0.5%	0.5%
$UPDRS\text{-}II_{ADL}$ (x, sd)	13.0 (6.9)	13.3 (6.7)	13.6 (6.6)	12.7 (6.0)	12.5 (6.0)	11.7 (6.1)
$UPDRS\text{-}III_{Motor}$ (x,sd)	26.7 (14.5)	27.2 (13.9)	27.5 (12.1)	27.3 (12.0)	25.8 (11.8)	26.1 (11.7)
L-dopa$_{baseline}$ (mg/day)	700	600	600	750	750	750
Previous Anti-Parkinson medication						
Dopaminergic agents				100%	99.5%	100%
Dopa and dopa derivatives	100	100	100	99.0%	99.5%	100.0%
Other dopaminergics	1.7%	4.2%	2.7%	12.1%	27.8%	23.3%
Dopaminergic $_{not\ specified}$	-	-	-	11.1%	6.3%	9.4%
Dopamine agonists	0.8%	1.7%	2.7%	5.1%	3.9%	3.0%
Anticholinergic agents	7.5%	16.9%	6.3%	10.1%	11.7%	6.4%
Amandatine deriv.	14.2%	14.4%	15.3%	21.2%	17.1%	18.3%
MAO- B inhibitors	16.7%	19.5%	14.4%	15.2%	20.0%	13.9%

n_{ss} indicates the safety data set , n_{FAS} indicates the full analysis data set
sd: standard deviation; Amandatine deriv.: Amandatine derivatives

Exposure

The actual doses received and concomitant anti-Parkinson medication used are presented in below table. In study SP650, the target dose was reached in 75% and 68% of the subjects for the 18 mg/day dose arm and the 27 mg/day dose arm, respectively.

Table 10. Doses and concomitant anti-Parkinson medication

	SP650			SP515		
	Placebo	Rotigotine 18 mg/day	Rotigotine 27 mg/day	Placebo	Rotigotine	Pramipexole
n_{ss}	120	118	111	99	205	202
Rotigotine / Pramipexole xx cm^2 / xx caps = xx mg / xx mg						
20 cm^2 / 3 caps 9.0 mg / 0.375 mg	n.a	4.2%	5.5%	0.0%	2.4%	1.0%
30 cm^2 / 3 caps 13.5 mg / 0.75 mg	n.a	16.0%	11.9%	1.0%	6.3%	5.4%
40 cm^2 / 3 caps 18.0 mg / 1.50 mg	n.a	74.8%	4.6%	2.0%	7.8%	1.9%
50 cm^2 / 6 caps 22.5 mg / 2.25 mg	n.a		10.1%	4.0%	8.8%	15.3%
60 cm^2 / 6 caps 27.0 mg / 3.00 mg	n.a		67.9%	16.2%	15.6%	18.3%
70 cm^2 / 9 caps 31.5 mg / 3.75 mg		n.a		10.1%	10.7%	10.9%
80 cm^2 / 9 caps 36.0 mg / 4.50 mg				53.5%	43.9%	31.7%
Anti-Parkinson medication during the trial						
Any	100%	100%	100%	100%	100%	100%
Dopa (derivatives)	100%	100%	100%	100%	100%	100%
COMT-inhibitor	-	1.7%	-	12.1%	28.8%	25.2%
Adamantane derivatives	14.1%	14.4%	16.2%	21.2%	17.1%	18.3%
MAO-B inhibitors	16.7%	18.6%	14.4%	14.1%	19.5%	14.4%
Benserazide	-	-	-	11.1%	6.8%	9.4%
Dopamine agonists	1.7%	2.5%	2.7%	1.0%	3.4%	1.5%
Anticholinergic agents	7.5%	16.9%	6.3%	10.1%	11.7%	9.4%
Dose adaptations L-dopa during maintenance	7.6%	9.7%	13.8%	2.1%	0.5%	0.5%

nss : safety data set, caps: capsules, n.a: not applicable

Efficacy results

Efficacy – Primary Endpoint

Table 11. PRIMARY EFFICACY– Responder rates

	SP650			SP515		
	Placebo	**Rotigotine** 18 mg/day	**Rotigotine** 27 mg/day	**Placebo**	**Rotigotine**	**Pramipexole**
n_{FAS}	119	113	109	100	201	200
Subjects with ≥ 30% reduction in OFF time	**34%**	**57%**	**55%**	**35%**	**60%**	**67%**
Difference		22.2%	20.6%		24.7%	32.0%
$CI_{95\%\ difference\ vs.\ placebo}$		9.7% ; 34.7%	7.9% ; 33.3%		13.2% ; 36.3%	20.6% ; 43.4%
p value		p <0.001	p <0.001		p < 0.001	p < 0.001
Difference			-0.02		-7.3%	
$CI_{95\%\ difference\ vs.\ active}$			-14.6 ; 11.5		-16.7% ; 2.1%	
p value			n.a		n.a	

n_{FAS} : full analysis set, n.a: not applicable

Efficacy- Secondary Endpoints

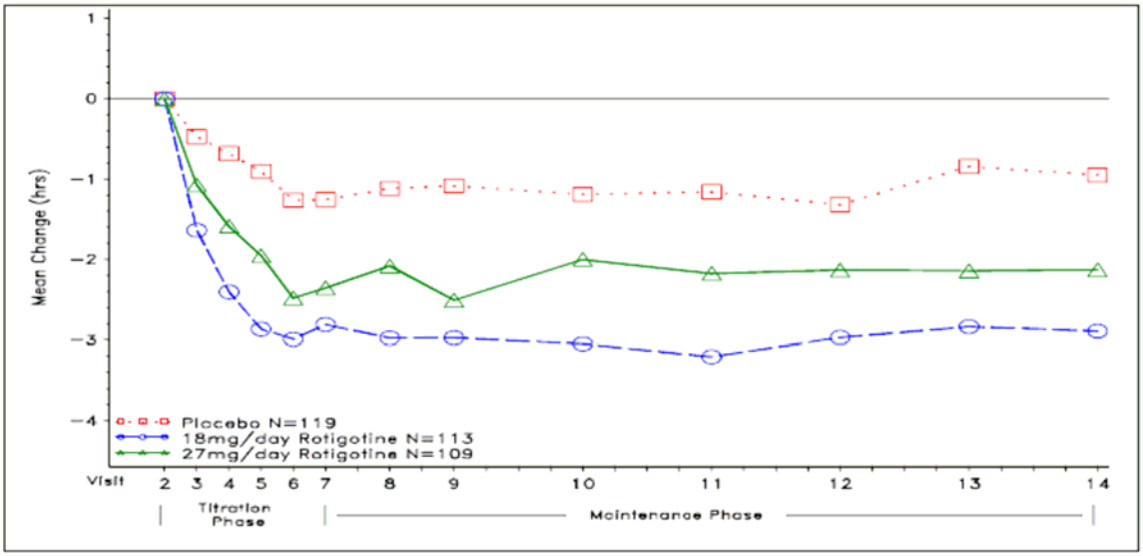
Table 12. SECONDARY EFFICACY – main secondary endpoint : absolute change in 'off' time

	SP650			SP515		
	Placebo	**Rotigotine** 18 mg/day	**Rotigotine** 27 mg/day	**Placebo**	**Rotigotine**	**Pramipexole**
n_{FAS}	119	113	109	100	201	200
OFF-time (hrs)						
Baseline	6.4	6.8	6.3	6.6	6.2	6.0
End of maintenance	5.5	3.6	3.5	5.5	3.8	3.3
Change	-0.9	-2.7	-2.1	-0.88	-2.46	-2.81
Difference		-1.8	-1.2		-1.58	-1.94
$CI_{95\%\ difference\ vs.\ active}$		-2.6 ; -1.0	-2.0 ; -0.4		-2.27 ; -0.90	-2.63 ; -1.25
p value		p< 0.001	p = 0.003		p < 0.0001	p < 0.0001
Difference			-0.6			-0.35
$CI_{95\%\ difference\ vs.\ active}$			-0.29 ; 1.49			-0.91; 0.21
p value			n.a			n.a

n_{FAS} : full analysis set, n.a: not applicable

Figure 1

Mean change in absolute "off" time (hours) by visit in SP650 (FAS with LOCF)



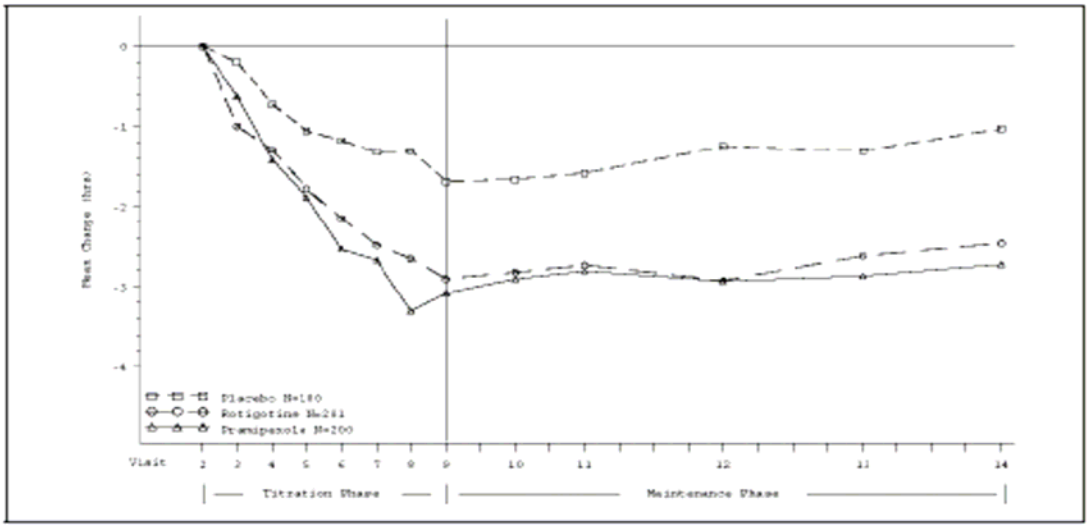
FAS=Full Analysis Set; LOCF=Last Observation Carried Forward

Visit 2 = Baseline; Visits 3, 4, 5, and 6 correspond to the beginning of dose Titration Phase Weeks 2, 3, 4, and 5, respectively; Visits 7, 8, 9, 10, 11, 12, 13, and 14 correspond to the beginning of Maintenance Phase Weeks 1, 3, 5, 9, 13, 17, 21 and 25, respectively.

Data Source: Figure 4

Figure 2

Mean change in absolute "off" time (hours) by visit in SP515 (FAS with LOCF)



FAS=Full Analysis Set; LOCF=last observation carried forward

Note: Visit 2 = Baseline; Visits 3, 4, 5, 6, 7 and 8 correspond to Titration Phase Weeks 2, 3, 4, 5, 6, and 7, respectively; Visits 9, 10, 11, 12, 13, and 14 correspond to Maintenance Phase Weeks 0, 2, 4, 8, 12, and 16, respectively.

Data Source: Figure 6.1

Table 13. SECONDARY EFFICACY – Other endpoints (only presented using descriptive statistics)

	SP650			SP515		
	Placebo	**Rotigotine** 18 mg/day	**Rotigotine** 27 mg/day	**Placebo**	**Rotigotine**	**Pramipexole**
n_{FAS}	119	113	109	100	201	200
% Change in OFF	-15.7%	-42.6%	-32.4%	-12.9%	-38.1%	-44.2%
ON-time –overall (hrs)						
Baseline	9.6	9.2	10.1	9.4	9.8	10.0
End of maintenance	10.7	12.3	12.4	10.3	12.2	12.7
Change	1.1	3.1	2.3	0.9	2.4	2.6
ON-time + dyskinesias						
Baseline	1.2	1.2	1.1	1.2	1.4	1.5
End of maintenance	1.2	0.8	1.2	0.7	1.0	1.5
Change	-0.1	-0.5	+0.1	-0.5	-0.4	0.0
UPDRS-II						
Baseline	13.1	13.4	13.6	12.8	12.3	12.1
Change EOM	-0.5	-3.1	-3.2	-2.0	-4.2	-4.6
UPDRS-III ON state						
Baseline	26.7	27.4	27.7	26.8	26.3	26.4
Change EOM	-3.4	-6.8	-8.7	-4.3	-8.7	-10.3
L-dopa+ (mg/day)						
Baseline (x)	752.9	759.5	740.5	814.1	794.8	812.9
EOM (x)	736.7	732.4	707.1	805.3	773.2	736.5
%% change (x, sd)	-1.6% (11.1%)	-2.6% (9.6%)	-3.9% (12.8%)	-0.9% (7.6%)	-3.3% (11.0%)	-7.8% (20.5%)
CGI-investigator						
Very much improved	4%	11%	12%	4.2%	10.7%	16.3%
Much improved	23%	35%	38%	23.2%	40.1%	38.8%
Minimally improved	25%	28%	20%	21.1%	32.5%	24.0%
No change	26%	11%	13%	34.7%	12.7%	13.8%
Minimally worse	15%	9%	11%	12.6%	3.0%	3.1%
Much worse	5%	6%	6%	4.2%	1.0%	3.6%
Very much worse	2%	0%	1%	0.0%	0.0%	0.0%

EOM: end of maintenance, CGI: Clinical Global Impression

- **Supportive studies**

Two phase IIIb studies were provided, respectively, to evaluate the effect of overnight switching from ropinirole, pramipexole, or cabergoline to rotigotine (SP824) and the effect of rotigotine on early morning motor impairment and sleep disorders (SP826).
In study SP824, subjects switched from an oral dopamine agonist to rotigotine transdermal experienced no loss of efficacy or increase in sleeps impairment.
In study SP826, treatment with transdermal rotigotine improved early morning motor impairment and sleep disorders in subjects who were diagnosed with idiopathic Parkinson's disease and who were titrated to an optimal dose of rotigotine up to 36mg/day. In addition, the CGI (Clinical Global Impression), PGI (Patient Global Impression), and PDQ-8 (Parkinson's Disease Questionnaire, short form) showed consistent improvement. An improved control of motor performance as supported by improvements in tapping Rates, UPDRS Part III Score, nocturnal akinesia score, and the standing-walking-turning test was observed. An improved control of sleep disorders was observed as supported by a decreased nocturnal akinesia, decreased nocturnal dystonia, decreased nocturnal cramps, fewer nocturias, an improved sleep and nocturnal disability score and an improved sleep without daytime somnolence.

- **Discussion on clinical efficacy**

The clinical development program of rotigotine, proposed by the applicant to extend the therapeutic indication to advanced stage Parkinson's disease is in accordance with the Note for Guidance on Clinical investigation of medicinal products in the treatment of Parkinson's disease (CPMP/EWP/563/95).

The design and conduct of the pivotal studies did not raise critical issues. Especially the complex double-dummy schedule applied in both pivotal studies was quite challenging. Furthermore, the management of concomitant medication was as expected in those studies performed in patients with advanced Parkinson's disease. One point of criticism is the predefined non-inferiority margin in the active controlled study (SP515). The predefined non-inferiority margin is questionable since in the worse case scenario as a loss of effect of 50% would in principle have been accepted.

Rotigotine was effective in reducing 'off' time as compared to placebo, irrespective of whether this was expressed in terms of responders, defined as a subject with a ≥ 30% decrease in absolute time spent 'off', or absolute change in 'off' time.

In study SP650, responder rates were 55%, 57% and 34% for rotigotine 27 mg/day, rotigotine 18 mg/day and placebo respectively. The 'off' time decreased from baseline by 2.1, 2.7 and 0.9 hours for rotigotine 27 mg/day, rotigotine 18 mg/day and placebo respectively.
In study SP515, responder rates were 67%, 60% and 35% for pramipexole, rotigotine and placebo respectively. The 'off' time decreased by 2.5, 2.8 and 0.9 hours for rotigotine, pramipexole and placebo respectively.

Differences with placebo were all highly significant and a reduction in 'off' time of 2 hours as compared to placebo was clinically relevant.
Nevertheless, non inferiority has not been demonstrated even wih a predefined non-inferiority margin considered to be set too high. The lower limit of the confidence interval of the difference in responder rates exceeded the non-inferiority margin of 15% ($CI_{95\%}$: -16.7%; 2.1%). In contrast, the confidence interval of the difference in the absolute change in the 'off' time between rotigotine and pramipexole was within the predefined non-inferiority margin i.e. 1.2 hrs ($CI_{95\%}$: -0.91; 0.21). Although these results appeared controversial, a clinical benefit of rotigotine in the 'on' time without dyskinesia was also observed, as compared to pramipexole.

With respect to the open label and uncontrolled studies SP824 and SP826, results do not allow any conclusions concerning the overall efficacy of rotigotine and efficacy variables such as improvement in sleep (as measured by the Parkinson's disease sleep scale or PDSS, and Epworth Sleepiness Scale or ESS). The limitation of these efficacy results was acknowledged by the MAH as only descriptive statistics were presented.

Overall, the efficacy results from the clinical development program of Neupro are supportive of the applied extension of indication to include the treatment of the signs and symptoms of advanced idiopathic Parkinson's disease 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).

Clinical Safety

All subjects receiving at least 1 dose of trial medication (rotigotine silicone patch formulation, pramipexole, or placebo) were included in the safety analyses.

The safety results presented mainly concern the primary analysis set, i.e. all subjects from the pivotal studies SP650 and SP515.
Safety variables included the occurrence of adverse events, changes in vital signs, body weight, ECGs, clinical laboratory values, physical and neurological examination, Epworth Sleepiness Scale scores and Parkinson's Disease Sleep Scale (SP515 only).

- Patient exposure

Overall, 1151 subjects with advanced-stage Parkinson's disease were exposed to rotigotine (see Table 14).

Table 14. Summary of Rotigotine exposure

Pool features :	**Pool AS1 n=434 Phase III /DB**	**Pool AS2 n=827 Phase II/III exclusive OL**	**Pool AS3 n=1151 Phase II/III inclusive OL**	**Pool AS4 n=653 DB + OL data**	**Pool AS5 N=653 OL data-only**
Treatment duration (days, mean ± SD)	163.0±56.41	117.9±65.09	347±334	529.2±341.59	435.5±300.07
Mean daily dose (mg/day, mean ± SD)	21.7±6.84	19.3±8.35	22.1±8.32	25.4±6.02	25.7±6.35
Maximum daily dose (mg/day, mean ± SD)	24.7±8.08	23.2±10.24	26.7±9.54	29.8±6.52	29.1±6.85
Daily dose of longest duration (mg/day, mean ± SD)	23.7±8.51	22.2±10.66	24.4±9.96	27.1±7.49	27.1±7.48

Set AS1 primary analysis set, included all subjects in the double blind of the pivotal studies i.e. studies SP650 and SP515.
Set AS2 included all subjects with advanced-stage Parkinson's diseases in the phase 2/3 trials excluding the open-label extension data i.e. studies SP533, SP591, SP824, SP826, SP511, SP515 and SP650.
Set AS3 is an extension of AS2 included the open-label data as well.
Set AS4 includes all subjects with advanced-stage Parkinson's disease treated in the pivotal studies and treat at least once in the open-label extension: SP515 + SP516 and SP650DB + SP650OL.
Set AS5 included the same subjects as in set AS4, but only the open-label data were used.

- Adverse events (AEs)

Aside from those events that are associated with the method of administration (i.e. use of transdermal patch), the reported AEs mainly concern those generally considered as class-related and well-known pharmacodynamic effects of dopamine agonists. Of importance, no dose relationship was observed between rotigotine dose and the occurrence of the AEs.

Table 15. Adverse events occurring in at least 5% of rotigotine-treated subjects during treatment (Pool AS1)

System organ class/preferred term	Placebo n=219	Rotigotine n=434	Pramipexole. n=202
Any system organ class with AEs in ≥ 5% of subjects	***62.6%***	***73.0%***	***70.3%***
Gastrointestinal disorders	***20.1%***	***27.4%***	***15.8%***
Nausea & Vomiting	17.4%	22.6%	12.9%
Nausea	15.5%	21.2%	12.9%
Vomiting	5.0%	7.1%	0.0%
Constipation	5.0%	5.5%	4.0%
General disorders and administration site conditions	***20.1%***	***39.9%***	***11.9%***
Application and instillation site reactions	11.9%	31.3%	8.4%
Application site erythema	4.1%	14.5%	4.0%
Application site pruritus	3.7%	12.4%	3.0%
Application site dermatitis	0.5%	4.6%	0.5%
Oedema peripheral	1.4%	7.8%	2.5%
Asthenic conditions[A]	***8.7%***	***5.1%***	***2.0%***
Infections and infestations (All URTI)	***8.7%***	***8.8%***	***3.5%***
Nasopharyngitis	3.2%	5.1%	2.0%
Injury, poisoning and procedural complications	***13.7%***	***10.8%***	***2.5%***
Fall	11.0%	8.3%	2.5%
Musculoskeletal and connective tissue disorders	***18.3%***	***16.4%***	***9.9%***
Back pain	4.1%	5.3%	8.4%
Arthralgia	4.6%	6.7%	1.0%
Nervous system disorders	***40.6%***	***47.0%***	***38.6%***
Somnolence	18.7%	22.8%	11.9%
Dyskinesia	5.0%	13.6%	15.3%
Dizziness	12.8%	14.7%	10.9%
Headache	6.8%	7.4%	6.9%
Psychiatric disorders	***6.8%***	***15.0%***	***11.9%***
Dist. in initiating and maintaining sleep	5.0%	8.3%	5.0%
Insomnia	5.0%	7.6%	4.5%
Perception disturbances	1.8%	7.6%	6.9%
Hallucination	1.8%	5.5%	4.0%

The rates of AEs for rotigotine and pramipexole are comparable. Any differences in numerical values are probably due to random variation.

- Deaths and other serious adverse events

There were 20 reports of deaths. These concerned patients who received rotigotine (n=16), placebo (n=3) and no medication (n=1, the death occurred during the run-in period). The reported deaths under medication were not considered related to study treatment. The causes of death under rotigotine were: cerebrovascular accident (n=3), myocardial infarction (n=2), pneumonia (n=2), completed suicide (n=2), cardiac disorder(n=1), renal cancer metastatic(n=1), unexplained death(n=1), road traffic accident(n=1), bronchial carcinoma(n=1), intestinal obstruction (n=1) and pulmonary embolism(n=1).

Forty-six (9%), 33 (9%) and 16 (7.4%) serious AEs were reported in the rotigotine, placebo and pramipexole groups, respectively.

Serious treatment-emergent adverse events related to rotigotine medication included: myocardial ischemia (0.2%), atrial fibrillation (0.2%), supraventricular tachycardia (0.2%), nausea (0.2%), application and instillation site reactions (0.5%), application site dermatitis (0.5%), Oedema peripheral (0.2%), cellulitis (0.2%), fall (0.2%), dyskinesia (0.2%), vasovagal syncope (0.2%), and sleep attacks (0.2%). No serious adverse events were reported with respect to hallucination, psychosis, paranoid reaction, or somnolence.

- Other safety findings

Among all rotigotine-treated subjects there were 514 application and instillation site reactions reported by 334 out of 1151 subjects (29%).

Oedema was reported in 1% of placebo-treated subjects and 9% of rotigotine-treated. Two subjects (<1%) in the rotigotine group had severe peripheral oedema, one case was reported as serious and resulted in discontinuation of treatment. Three additional rotigotine-treated subjects (<1% total) discontinued treatment as a result of peripheral oedema.
The rate of oedema was higher in study SP650 (placebo<1%, rotigotine=13%) as compared to study SP515 (placebo=2%, rotigotine=4%, pramipexole=3%).
In clinical studies, the 6 month-specific rates of peripheral oedema remained at about 4% through the entire observation period up to 36 months.

- Discontinuation due to adverse events

Adverse events lead to discontinuation in 8% of the placebo-treated subjects and 13% of the rotigotine-treated subjects.
Adverse event terms that resulted in discontinuation of >1% of rotigotine-treated subjects included nausea (4%), vomiting (2%), and application and instillation site reactions (2%). Peripheral Oedema lead to discontinuation in the Rotigotine group (0.9%).

Dose reduction due to AE occurred in 3% of subjects receiving placebo and in 5% of subjects receiving rotigotine. In the rotigotine group, the most frequent AE leading to dose reduction was dyskinesia (3%).

- **Discussion on Clinical Safety**

The safety profile of rotigotine in advanced Parkinson's disease is similar to the one observed for a dopamine-agonistic agent. Although the rotigotine doses were higher in this patient population, no dose-response relationship with respect to AEs was present. In addition, an increased frequency of AEs was observed as compared to monotherapy.

In studies SP650 and SP515, high incidence of application site reactions (31%) has been observed. Although these AEs may counteract the convenience gained by the once dosing schedule, they have similarly been reported in the monotherapy studies and therefore did not raise any new concern. Most application and instillation site reactions were mild or moderate in intensity, and most had resolved by the end of double-blind treatment. The incidence of these AEs did not appear to be dose dependent.

Safety analysis of specific issues such as cardiac arrythmias, eye disorders, severe application site reactions, oedema, orthostatic hypotension, dyskinesias, sleep attacks, compulsive behaviour, and potential for QT prolongation were performed in patients with advanced stage Parkinson’s disease from those clinical studies. No concerns were raised. In clinical studies, the 6 month-specific rates of peripheral oedema remained at about 4% through the entire observation period up to 36 months.

1.4 Pharmacovigilance

- **Risk Management Plan**

The MAA submitted an updated risk management plan.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risks		
Application site skin reactions	• Routine pharmacovigilance • Post-approval safety study under conditions of routine clinical practice. Particular attention will be paid to severe application site reactions (defined as events of special interest per protocol). • 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.) • Section 4.2 of the SPC provides important information on the method of administration • Listed as ADR in section 4.8
Sleep attacks and somnolence	• Routine pharmacovigilance • Post-approval safety study under conditions of routine clinical practice. Particular attention will be paid to sleep attacks (defined as events of special interest per protocol). • Additional information from ongoing clinical trials	• Warning in sections 4.4 and 4.7 of the SPC • Listed as ADR in section 4.8
Postural and orthostatic hypotension	• Routine pharmacovigilance • Post-approval safety study under conditions of routine clinical practice. • Additional information from ongoing clinical trials	• Warning in section 4.4 of the SPC • Listed as ADR in section 4.8
Compulsive disorders	• Routine pharmacovigilance • Post-approval safety study under conditions of routine clinical practice. • Additional information from ongoing clinical trials	• Warning in section 4.4 of the SPC • Listed as ADR in section 4.8

Potential risks		
Cardiovalvular fibrosis	• Routine pharmacovigilance • Post-approval safety study under conditions of routine clinical practice. Particular attention will be paid to valve fibrosis-related signs and symptoms (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	• Warning in section 4.4 of the SPC
Effects on retina	Routine pharmacovigilance Post-approval safety study under conditions of routine clinical practice Additional information from ongoing clinical trials	• Warning in section 4.4 of the SPC
Neuroleptic malignant syndrome after abrupt withdrawal	Routine pharmacovigilance Post-approval safety study under conditions of routine clinical practice Additional information from ongoing clinical trials	• Warning in section 4.4 of the SPC
Missing information		
Patients with severe hepatic impairment	Routine pharmacovigilance	• Warning in section 4.4 of the SPC

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.

1.5 Overall Conclusions and benefit/risk assessment

Based on the CHMP review of safety and efficacy, the CHMP considers that the benefit-risk for Neupro transdermal patches indicated in '*the treatment of the signs and symptoms of advanced idiopathic Parkinson's disease 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)*', is favourable and recommended the variation to the marketing authorisation.

A revised risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product.