SCIENTIFIC DISCUSSION

1.1 Introduction

Neupro is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease. Neupro contains rotigotine, a new dopamine agonist, and is formulated 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. Treatment should be initiated at 2 mg/24 h and then increased in weekly increments of 2 mg/24 h to an effective dose up to a maximal dose of 8 mg/24 h.

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 is a new chemical substance belonging to the group of non-ergolinic dopamine agonists. It shows a close structural analogy to dopamine and apomorphine. Rotigotine has been developed as transdermal patch to treat Parkinson's disease.

1.2 Quality aspects

Introduction

Neupro is 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.
Each patch is composed of three layers:

- a non removable backing layer, which consists of a siliconised, aluminised, colour coated and imprinted polyester film,
- a self adhesive matrix layer containing rotigotine, poly(dimethylsiloxane, trimethylsilyl silicate)-copolymerisate, povidone, sodium metabisulphite, ascorbyl palmitate and α-tocopherol,
- a removable protective layer, which is a transparent fluoropolymer coated polyester film.

Each transdermal patch is packed in a sachet (paper/LDPE/alu/ET copolymer PET/Alu/ ET copolymer/paper) placed in a cardboard carton. The different strengths are available separately and also as a treatment initiation pack containing 7 transdermal patches of each strength.

Active substance

Rotigotine is a new non-ergolinic dopamine agonist.
It is a white to off-white powder. Its water solubility and lipophilicity are pH dependent: at neutral pH it is poorly water-soluble and lipophilic (neutral form) and at more acidic pH rotigotine's water solubility increases and its lipophilicity decreases (protonated form).
It contains one chiral centre and it is synthesised solely as the *S*-isomer. No polymorphism has been observed during development. Rotigotine appears to be sensitive to oxidation and it is not hygroscopic.

- Manufacture

Rotigotine is synthesised by a 5-step process from 3 starting materials. Satisfactory specifications and associated methods have been provided for the starting materials, key intermediates, reagents and solvents.
The chiral centre is introduced through the use of a key starting material and it is not affected by the synthesis. Moreover, chiral purity is controlled as part of the active substance specification.
A number of synthetic processes have been used to produce batches used in non-clinical/clinical studies. No significant differences between lots obtained by the different processes have been noted, especially in term of impurity profile.Satisfactory validation data on 3 consecutive commercial scale batches have been provided and confirm the robustness of the process.

- Specification

The active substance specification includes tests for appearance, odor (PhEur), identity (IR, HPLC), melting point (PhEur), assay (HPLC), impurities (HPLC), chiral purity (chiral HPLC), optical rotation, residual solvents (GC), heavy metals (PhEur), sulfated ash (PhEur) and water content.
Impurity limits in the specification are justified by toxicology studies.
Batch analysis data provided for the three validation batches confirm satisfactory compliance and uniformity with the proposed specification.

- Stability

Under accelerated conditions (40°C/75% RH - commercial packaging) and long term conditions (25°C/60% RH - commercial packaging), respectively 6-month data and up to 18-month data have been provided for two primary stability batches manufactured according to the synthesis route at the commercial synthesis site.
The parameters tested included appearance, assay, melting point, purity and chiral purity.
The proposed retest period is supported by the presented data when rotigotine is stored in commercial packaging.

Medicinal product

- Pharmaceutical Development

Due to an extensive first-pass effect, rotigotine showed a very low bioavailability (below 1%) in rodents after oral administration. Based on rotigotine suitable physico-chemical properties for delivery through the skin (see active substance), a transdermal formulation has been developed to avoid the first-pass effect after oral administration and to enable continuous drug administration over 24 hours. A matrix transdermal patch, where the active is in the adhesive through which it diffuses to the skin surface, has been selected in order to keep the patch size as small as possible and to allow an easy application to the skin.

The acrylic patch formulation initially developed was replaced by a silicone formulation on grounds of superior bioavailability (see clinical section)The matrix layer
comprises a mixture of two commercially available amine compatible silicone-type pressure-sensitive adhesives for which satisfactory data on composition, manufacture, control and toxicology have been provided (see non clinical section). Their ratio in the patch has been investigated during development in order to obtain an optimised adhesion/cohesion balance. Moreover, the adhesives inertness and their absence of physical/chemical incompatibility with rotigotine as well as their local tolerance (see non clinical section) has been confirmed during development studies.
Different *in vitro* methods have been used during development and compared with *in vivo* pharmacokinetic data in order to evaluate a possible *in vitro/in vivo* correlation and the suitability of dissolution methods for routine control (see Product Specification).

The drug load in the patch (0.45 mg/cm^2 equivalent to about 50% surplus compared to the labeled strength) has been justified based on apparent drug release data determined by analyzing the

remaining content of used patches. It ensures a constant thermodynamic activity of the drug in the matrix over the intended application period.

Since rotigotine is sensitive to oxidation, 3 antioxidants have been added to the matrix so as to prevent oxidative degradation: sodium metabisulfite, α-tocopherol and ascorbyl palmitate.

The backing film consists of a polyethylene terephthalate film siliconised on its inner side, aluminised and coated with a pigment layer on the outermost. The siliconised inner surface provides a good anchorage for the matrix avoiding occurrence of adhesive residues on the skin after patch removal and no migration between the matrix layer and backing layer is expected.
The release liner consists of a transparent polyester foil. Stability data confirmed that significant migration of rotigotine into the protective foil can be excluded.

Compatibility of rotigotine with the adhesives, povidone, antioxidants, solvents, backing film and release liner has been confirmed. All the excipients are of PhEur quality except the silicone adhesives, the backing film and the release liner, for which satisfactory specifications have been defined. Regarding the TSE risk, Neupro does not contain any ingredient of ruminant origin.

The primary packaging material is a sachet composed of two heat sealable foils composed of the following layers (1 foil: (outside) paper, LDPE, aluminium, ethylene copolymer (inside) 1 foil: (outside) paper, ethylene copolymer, aluminium, polyethylene (inside)). It is in line with the European requirements for primary packaging materials.

The commercial formulation was used for the dose finding study and the 2 pivotal trials.

- Manufacture of the Product

The manufacturing process involves the following operations: preparation of the drug containing adhesive, coating onto the protective liner, evaporating the solvents, laminating the backing film onto the uncovered surface area of the dry adhesive matrix, cutting of the patches and heat-sealing of the sachets around the patches..
Satisfactory operating parameters and in-process controls have been defined at each stage of manufacture.
Satisfactory validation data provided for batches up to commercial scale confirm the robustness and reproducibility of the manufacturing process including packaging.

- Product Specification

The product specification includes tests controlled by validated methods for appearance (backing film, matrix, protective liner, sachet), adhesive properties,, tightness of the primary packaging, weight of the matrix, identity (UV and HPLC), identity of α-tocopherol, assay (HPLC), assay α-tocopherol, residual solvents (GC), degradation products (HPLC), dissolution, content uniformity (PhEur) and microbial purity (PhEur).
Batch analysis data provided for batches manufactured at the proposed commercial manufacturing site comply with the specifications and indicate consistent and reproducible manufacture.

- Stability of the Product

A matrixing design has been used for the stability studies of the different strengths. Under long-term conditions (25°C/60%RH – commercial packaging) and under accelerated conditions (40°C/75% RH - commercial packaging) respectively up to 2 year-data and 6-month data have been provided.
The parameters tested included appearance, adhesive properties, tightness of the primary packaging, weight of the matrix, residual solvents, purity, dissolution, assay, content uniformity and microbial purity.
Stress testing on patches with or without sachets under various conditions (high temperatures 80°C, humidity, oxidation and light, cycling testing (storage alternating daily between 4°C and 40°C/75% RH)) has been performed. Photostability studies have shown that the medicinal product is not light sensitive.

No significant changes have been observed under long-term conditions and the results presented support the proposed shelf life and storage conditions defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The active substance is well characterised and documented. The pharmaceutical form selected is adequate taking into account the properties and the stability of the active substance. The excipients are commonly used for this kind of formulation and the packaging material is well documented. The manufacturing process ensures to obtain reproducible finished product batches. Stability tests under ICH conditions indicate that the product is stable for the proposed shelf life.
At the time of the CHMP opinion there were some minor unresolved quality issues which had no impact on the benefit/risk profile. The applicant committed to provide the necessary information as follow-up measures within an agreed timeframe, and to submit variations if required following the evaluation of this additional information

1.3 Non-clinical aspects

Introduction

Rotigotine has been synthesized as a dopamine agonist for the treatment of PD. Its high lipophilicity and the rapid first pass metabolism made oral administration difficult; however, the same properties made it suitable for a transdermal delivery system.

Nonclinical studies with rotigotine were conducted in mice, rats, rabbits, and monkeys. Sufficient exposure multiples were achieved *in vivo* to allow comparison with clinical data, and in the calculation of safety margins.

Except for two repeated-dose toxicity and two local tolerance studies, all other pivotal studies were stated as performed in compliance with GLP. The data from the non-GLP studies were sufficiently supported by the GLP- compliant studies.

Pharmacology

- Primary pharmacodynamics (*in vitro/in vivo*)

A profiling program was performed to identify the receptor binding properties of rotigotine in detail using cloned human receptors where possible.

The dopamine (DA) receptor population in brain and periphery consists of several subtypes. For example, the postsynaptic D1 receptor and the D2-receptor which is located both pre- and postsynaptically. Later D3 and D4 receptors were identified, which are similar to D2. D3 receptors are highly expressed in limbic regions of the brain and less so in motor divisions (caudate/putamen). The Ki-value of dopamine, bromocriptine, quinpirole and 7-OH-DPAT for D3 receptors is respectively 25, 7.4, 5.1 and 0.8 nM and Ki-ratio D2/D3 is respectively 19, 0.7, 113 and 78 (i.e. quinpirole being most selective for D3). The D3 receptor is most widely cited in the inhibition of locomotor activity (D2 induces stimulation).

Rotigotine is an agonist at all dopamine receptors, showing highest affinity and highest activity via the D3 receptor. Rotigotine was found to preferentially bind to all dopamine receptors with a clear preference for the D3 receptor (Ki value of 0.7 nM versus 13-83 nM for D2 and D1). The affinities to the other dopamine receptors were found to be approximately 8 to 20-fold less for the D2, D4, D5 receptors or approximately 120-fold less for the D1 receptor. Ki-ratio D2/D3 of rotigotine is 19. Rotigotine also interacted with alpha2B, alpha2C, 5-HT1A, 5-HT7, and sigma receptors (Ki 27-149 nM), showed a minor interaction with monoamine transporters, but did not affect DA-metabolism in vitro.

In vitro, rotigotine exhibits both agonistic (D3, alpha1, 5-HT) and antagonistic (alpha2, M2) effects. It behaves as partial alpha2 agonist in the electrically stimulated mouse vas deferens and was shown to inhibit noradrenaline (and DA) release(IC_{50} of 48 nM).

Rotigotine induces stereotyped behavior (ED_{50} 0.53 mg/kg i.p. in rats) and enhanced motor activity in MPTP lesioned marmosets at ≥20 µg/kg s.c., where it restores locomotor activity and reduces disability with the locomotion resembling normal performance. With respect to contralateral rotations: at a dose of 6.2 µg/kg, rotigotine s.c., administered via minipump, is persistently effective in an animal model of PD (6-OHDA-lesioned rat). After i.v., i.p. and p.o. application, the functional activity was short lasting, but prolonged after s.c. or i.m. (bolus) treatment.

Phase 1 metabolites exhibit a binding profile similar to that of rotigotine. The R-enantiomer of rotigotine, exhibited a lower affinity to the DA-receptors than rotigotine. In *in vivo* models of PD (induction of stereotype behavior in rats or induction of contralateral rotations in 6-OHDA-lesioned rats), the R-enantiomer was inactive or behaved as partial agonist.
Concerning rotigotine metabolism, the phase 1 metabolites SPM 9206 (desthienylethyl-rotigotine) and SPM 9257 (despropyl-rotigotine) are not expected to contribute to the effects of rotigotine *in vivo*.

- Secondary pharmacodynamics

Some indications of antidepressant activity have been found for rotigotine (0.5-5 mg/kg s.c.), but it was difficult to discriminate from non-specific motor stimulation. Rotigotine shows no anti-anxiety activity. Rotigotine retains some dyskinesia-inducing potential and inhibits prolactin release *in vivo* (D2 agonism) in pig-tailed macaque monkeys.

- Safety pharmacology programme

Rotigotine (0-1 mg/kg s.c.) showed no effect on hexobarbital-induced sleeping time, but had nociceptive (ED50 0.9 mg/kg) and pro-convulsive activity (>0.1 mg/kg) in mice.

Rotigotine affected action potential duration and hERG-mediated potassium current at concentrations that far exceed (143 and 214 times, respectively) human unbound mean peak plasma concentrations achieved at 18 mg. In animal studies, rotigotine had some effect on blood pressure (anaesthetised rats 15% at ≥ 0.04 mg/kg i.v.) and heart rate (anaesthetised rats 12% reduction at ≥ 1 mg/kg i.v.). In conscious monkeys, single dysrhythmias such as distortion or reduction of the QRS complex were observed after injection of 0.03 mg/kg, and rotigotine induced transient biphasic responses with secondary sustained decreases of 20-40% in mean blood pressure that were dose-related (40% at 3 mg/kg i.v.) severe but transitory. Rotigotine did not accumulate in cardiac tissue further supporting the calculation procedure based on free plasma levels.

In the monkey, total radioactivity of labeled rotigotine was poorly distributed within the tissues and was rapidly eliminated with no apparent retention. Rotigotine at doses of 0.1 - 1 mg/kg s.c. elicited a reduction in urinary volume and electrolyte excretion in female rats.

- Pharmacodynamic drug interactions

No drug interaction studies were performed except for the interaction with L-dopa/carbidopa in rats and monkeys. Rotigotine 1, 3 or 10 mg/kg/48 h s.c. did not appear to augment the behavioral changes after co-administration with L-dopa/carbidopa.

Pharmacokinetics

When dosed intravenously, rotigotine has a short half life. An oily crystal suspension formulation of rotigotine for subcutaneous administration demonstrated sustained release effects when tested in rats and monkeys. When using the subcutaneous formulation, the kinetics are controlled by the absorption or release rate from the formulation, a phenomenon also observed in humans following patch application.

The transdermal route via silicone patches is relevant because this is the same route of administration as applied in the clinical situation. This route of exposure was however not suitable for performing toxicological studies, because of too much discomfort and skin lesions to the animals and possibly large interindividual variation in release of rotigotine from the patches.

- Absorption- Bioavailability

Results obtained with the patch administration in animals showed that the silicone based patch was superior to the acrylic based patch with respect to substance release. Following repeated dosing, 81 and 93 % substance was released from the silicone patch on the rat and monkey, respectively. The corresponding % release from the acrylic based patch was 28 and 22 %, respectively.

Subcutaneous dosing was applied in the toxicological studies. Although bioavailability was higher following this type of dosing, the plasma concentration profile in rats and monkeys following 1 administration over 24 or 48 hours was comparable to that in humans (1 silicone patch/24 hours).

The subcutaneous formulation resulted in a continuous systemic exposure in the animals over the dose periods of 24 or 48 hours and plasma concentrations increased with dose in a linear manner. When comparing the steady state plasma concentrations following administration of 1 mg/kg of the subcutaneous dose formulation to the mouse (normalized), rat, rabbit and monkey, the approximate Cmax values obtained were 2, 5, 16 and 3 ng/ml, respectively. In the clinical trial SP511 a normalized dose of 1 mg/kg of rotigotine in the patch resulted in an average Cmax plasma concentration of around 7 ng/mL and AUC values of around 140 h ng/ml. Pharmacokinetic safety ratios for the repeat dose toxicity studies were found to be 1 and 1-2 in the rat and monkey, respectively, when calculated from Cmax.

Safety ratios

Maximum therapeutic dose	**Dose**	**Cmax**	**AUC(daily)**
	40 cm^2 / 24 hour	2.1 ng/mL	38 h ng/mL
Repeat dose toxicity studies	**NOEL[a] or MTD[b](mg/kg)**	**Safety ratio Cmax**	**Safety ratio AUC**
Rat, 6 months	0.5[a]	1	0.5
Monkey, 12 months	1[a]	1-2	1
Carcinogenicity studies			
Mouse	30[b]	13	10
Rat	3[b]	3	3
Reproductive and developmental studies			
Mouse, Segment II	30[a] fetus	31	-
Rat, Segment I	>15[a] male	>25	-
Rat, Segment I	1.5[a] female	2	-
Rat, Segment II, teratogenicity	1.5[a] fetus	2	2
Rabbit, Segment II	25[a] (fetus)	235	221

- = Insufficient samples collected for calculation of AUC. Repeat dose toxicity studies, rat dosed every 48 hours, monkey very 24 hours. Carcinogenicity studies, animals dosed every 48 hours. Reproductive and developmental studies, animals dosed every 24 hour.

- Distribution

Only single and no repeated-dose tissue distribution studies were conducted as no target organs had been observed in the toxicological studies, which are not related to the pharmacodynamic or dopamine agonistic properties of rotigotine. Rotigotine and its metabolites were distributed to a wide variety of tissues, but in most cases also rapidly cleared. Long exposure times were observed in pigmented eye and fur in rats. Relatively high concentrations of radioactivity were measurable in adrenals, kidneys and Harderian gland, and in monkeys additionally in the prostate gland and the eye. From studies in the rat and monkey, the prostate gland and the adrenals were identified as pharmacokinetic target organs for potential compound-related side effects when in clinical use. Therefore, these organs were carefully investigated in the toxicology studies by histopathology.

The compound binds to melanin giving rise to high concentrations of compound in the pigmented eye and skin.

Binding of rotigotine to plasma proteins ranged between 86 and 92 % in the mouse, rat, monkey and human. Binding at therapeutic plasma concentration in human plasma was found to be ca. 90 %.

Rotigotine crosses the placenta and exposes the fetus when dosed to pregnant animals.

Combining the tissue and brain distribution studies with the in vivo metabolism identification study in the monkey, estimates of human brain concentrations of rotigotine could be made. Following a 1-hour intravenous infusion of 1 mg/kg of rotigotine to the monkey, brain rotigotine concentrations up to around 320 ng/ml may be reached. By analogy, brain concentrations of the SPM 9206 metabolite up to 36 ng/ml may be achieved. In the monkey, the ratio of the brain over the plasma concentration for rotigotine is around 5. Having a maximum therapeutic plasma concentration of 2.1 ng/ml in patients and assuming the ratio of the brain over plasma concentration ratio is identical in human and monkey, human brain concentrations up to 10 ng/ml may be achieved for rotigotine when in clinical use.

- Metabolism (*in vitro/in vivo*)

Following absorption rotigotine was rapidly metabolised. Three phase 1 metabolites showed pharmacological activity. However, pharmacokinetics of these metabolites were not required as their presence in plasma was too low.

The major metabolite observed in animal hepatocytes, the glucuronide conjugate of rotigotine, was in vivo excreted into bile and only reached the blood system at low levels. Conjugates of the N-dealkylated metabolites were found to be the major metabolites in plasma. Following subcutaneous administration, the sulfate and the glucuronide conjugates of the SPM 9206 metabolite and the sulfate conjugates of the SPM 9257 and the sulfate of the desthienylethyl despropyl metabolite were found to be the major metabolites in plasma. In human plasma, the sulphate conjugates of rotigotine, the SPM 9206 and the SPM 9257 metabolite were found to be the major metabolites. All the human major metabolites found in plasma were also found in the plasma of the main toxicological species.

CYP2C19 was found to be the major CYP isoform involved in the phase 1 metabolism of rotigotine. However, multiple CYP-isoforms appear to be capable of catalyzing the metabolism. In vitro studies suggest a low risk for drug-drug interactions with co-administered drugs which are substrates of CYP isoforms in vivo. Also, no induction of human liver CYP isoforms has been found. No potential for displacement of rotigotine by warfarin and vice versa was detected with human serum albumin in vitro. Rotigotine was found not to be a substrate for P-glycoprotein and does not modulate digoxin transport in vitro.

Rotigotine (S enantiomer) is a chiral substance. No studies were conducted in animal species for quantification of the R enantiomer, as its presence is considered to be unlikely for the following reasons: a) Rotigotine is unlikely to undergo racemization due to its chemical stability at the chiral center; b) The metabolic processes do not attack the chiral position of the molecule; and c) When analyzing human urine samples, the R-enantiomer was not found.

- Excretion

In rats, rotigotine and/or its metabolites are mainly excreted by biliary excretion into the feces. This route of excretion only is of importance in rats. In humans and monkeys, urinary excretion is the dominant route of excretion. Moreover, following intravenous dosing a short elimination half-life of approximately 1.8 hours in rats and 0.7 hours in monkeys could be observed. Therefore accumulation is not to be expected in case of constant release from patches or subcutaneous depots. Some studies, especially transdermal dosing in rats, give the impression of accumulation, but this is entirely due to increasing release of rotigotine.

Toxicology

The majority of pivotal repeated dose toxicity, all reproductive toxicity studies and carcinogenicity were conducted with an alternative oily crystal suspension by s.c. administration. Using this test article, plasma levels were achieved, which mimic those in humans after patch administration.

- Single dose toxicity

Only one non-GLP intravenous study in mice was submitted from which no meaningful conclusion can be drawn.

- Repeat dose toxicity

An overview of the pivotal repeat-dose toxicity studies is shown in the table below.

Pivotal Repeat-dose toxicity studies

Species/Sex/ Number/Group	Dose/Route (mg/kg/day[1])	Duration	NOEL/ NOAEL[1] (mg/kg/day)
Mouse 10/sex/gp + 15/sex/gp for toxicokinetics	SC[2]: 0, 3, 10, 30, 60/90[3] Per 48 hours	13 weeks	< 3 mg/kg/48 h
Rat 10/sex/gp + 9/sex/gp for toxicokinetics	IV (infusion): 0, 3, 8, 16, 24	28 days	NOAEL: 3
Rat 10/sex/gp + 6/sex/gp toxicokinetics + 5/sex/gp recovery	SC: 0, 1, 3, 10, 30 per 48 hours	13 weeks + 4 weeks recovery	NOEL: 1 mg/kg/48 h
Rat 20/sex/gp + 6/sex/gp toxicokinetics + 5/sex/gp recovery	SC: 0, 0.5, 2.5, 12.5 per 48 hours	6 months + 8 weeks recovery	M: NOEL 0.5 mg/kg/48 h F: NOAEL 0.5 mg/kg/48 h
Cyn.monkey 4-5/sex/gp, of which a few animals for recovery	IV (infusion): 0, 3, 8, 24/16[4]	28 days + 4 weeks recovery	NOAEL: 8
Cyn.monkey 3/sex/gp + 2/sex/gp for recovery	SC: 0, 0.25, 1, 4	3 months + 4 weeks recovery	NOAEL: 1
Cyn.monkey 4/sex/gp + 2/sex/gp for recovery	SC: 0, 0.25, 1, 4-16[5]	12 months + 8 weeks recovery	NOAEL: 1

[1] Unless stated otherwise
[2] Oily crystal suspension was used in subcutaneous administration, unless stated otherwise
[3] From week 8 onwards, 90 mg/kg/48 h was administered instead of 60 mg/kg/48 h.
[4] Due to severe toxicity at 24 mg/kg/day, treatment was stopped after 2-4 days. After 3-week wash-out, the animals were dosed with 16 mg/kg/day.
[5] The high dose was increased or decreased during the experiment due to missing or severe toxicity

The most prominent systemic effects such as restlessness, hyperactivity, ataxia, aggression, and, at very high dosages, self-mutilation, were observed and are mainly related to the mechanism of action. Treatment-related mortality occurred at exposures, which were at least 24 times the expected maximal

human exposure based on AUC values. In mice and rats, but not in monkeys, decreases in body weight gain and increases in food and water consumption were observed at exposures generally several times higher than the human exposure. In some rat studies, increased food consumption occurred at lower dosages than a decreased body weight gain. Spillage due to restlessness probably played a part. In rats, enlarged ovaries with an increased number of corpora lutea, stromal activation in the uterus, and a decreased pituitary weight can be considered a dopamine-agonist effect, due to the inhibition of the prolactin secretion.

Increased levels of ALT and AST were observed in rats, primarily in females, from an exposure of about 6 times the human exposure. No histopathological changes were reported in the liver of rats. The relevance of the increased AST values in female rats was questioned. Upon request, the Applicant has submitted individual data on relative liver weight of females at all dose groups and histopathology of high dose and control female groups (histopathology of mid and low dose group animals was not performed since the liver was not considered as a target organ). The medium values of relative liver weights did not differ among dose groups. When analysing the individual values presented a correlation between increased AST levels and relative liver weight could not be identified. Also, the (mild) histopathological findings in the liver of high dose group females did not show increased incidence or severity as compared to controls.

In monkeys, only in 1 study minimal centrilobular vacuolation was observed in the liver. No increases in liver enzymes were observed in monkeys.

The data presented seems to suggest that the liver should not be considered as a target organ for rotigotine-induced toxicity.

Severe decreases in blood pressure and a decreased heart rate were observed in 1 monkey study, at a very high intravenous dose only.

In rats, the lowest NOAEL in the subcutaneous pivotal studies was 0.5 mg/kg/48 h. In monkeys, the lowest NOAEL in the pivotal studies was 1 mg/kg/day. In both species, at these dosages, the exposure was approximately equal to, or slightly higher than the human exposure based on both AUC and Cmax data. The critical effects were mostly effects on body weight and food consumption in rats, and CNS effects in monkeys.

Effects on clinical biochemistry for some parameters in long-term studies in rodents are partly significant, but do not show a clear dose-or time- dependency and were mainly reversible during the recovery period. No such effects were determined in monkeys. Because of the absence of dose- or time-dependency and the lack of consistency over different studies in the same species and over different species, these effects were not regarded as relevant to humans.

(Regarding toxicokinetics, see above section “Phamacokinetics”)

- Genotoxicity *in vitro* and *in vivo* (with toxicokinetics)

The mutagenic potential of rotigotine was evaluated *in vitro* in bacterial and mammalian cell systems and *in vivo* in mouse bone marrow and rat hepatocytes for UDS analysis. A positive effect was observed *in vitro* in the mouse lymphoma assay where at the higher levels of rotigotine a clastogenic effect was observed, as revealed by increased mutations frequency in small colonies. *In vivo* studies did not reveal genotoxic potential. Since rotigotine was cytotoxic in this system and no *in vivo* mutagenic/clastogenic effect were observed, the relevance of the isolated positive *in vitro* effect is hard to evaluate and its relevance may be very low.

- Carcinogenicity

The carcinogenic potential of rotigotine was studied in rats and mice in 104-week studies.

In mice (subcutaneous doses up to 30mg/kg/48h), no test substance-related neoplastic effects were described and rotigotine can be considered as non-carcinogenic.

In rats (subcutaneous doses up to 3mg/kg/48h), Leydig cell hyperplasia and testis tumours were seen in all treated males. Uterus tumours were seen in mid- and high-dose females. A general decrease was noted in the incidence of tumours of the mammary gland. In both sexes, there was a decrease in the incidence of tumours in the pituitary (adenoma of the pars distalis). These tumor types are related to the decreased prolactin levels induced by rotigotine, similarly to other drugs of the same class. The accumulated mechanistic information of the compounds of the same class as well as the evidence that these events are not relevant for man lead also to the conclusion that rotigotine does not seem to pose a carcinogenic risk for man.

The local/tumorigenic effects of the patch itself have also been analysed in a repeated application study in mini pigs. The study revealed that there is a potential for some inflammatory reaction when the patch is applied successively in the same site, but this reaction is reduced when sites of application are changed at every application. Neoplastic lesions at the site of application were not observed.

- Reproduction Toxicity

The toxicokinetic studies have shown that rotigotine and/or its metabolites crossed the placental barrier with highest concentrations associated with the fetus, fetal liver, placenta and chorioallentoic placenta. The reproductive toxicity of rotigotine was studied in Segment I studies in mouse and rat, Segment II studies in mouse, rat and rabbit, and in Segment III studies in rat.

No substance-related findings were seen in rabbits. At high doses, rotigotine reduced the motility of the spermatozoa in rats, but none of the tested doses influenced the fertility of these animals. In rats, dopamine agonists, such as rotigotine, have a well-known effect on prolactin secretion. In the Segment I study in female rats, none of the rats became pregnant. Also in the Segment II study in rats, only 50 % of the animals at intermediate and none of the rats at the high dose became pregnant. In rats and mice, embryo-toxicity was seen at materno-toxic doses (postimplantation loss, embryo resorptions). In rats and rabbits, no teratogenic findings were seen. In one rabbit study, hyperflexion of the paws and crossed legs (bilateral) were noted in one litter at high dose (25 mg/kg). The values presented regarding historical control data support the argument that the limb malformations as well as the pre-implantation loss in he control group of the rabbit study were within the historical control range. It is therefore difficult to conclude about causal relationship of malformed limbs with the treatment. In mice at the highest dose of 90 mg/kg/48 hours, there was an increased incidence of missing ossification of the talus, incomplete ossification of the sternebrae and total skeletal retardations. No increase in incidence of malformations or variations was observed. In the Segment III study, pups from female rats exposed to rotigotine, in equal or slightly higher doses than the human exposure, showed a reduced auditory startle reflex, pupillary reflex or passive avoidance test. In addition, the time-point of the eye and ear opening, cleavage of the balanopreputial gland and the vaginal opening were significantly delayed. In the dams, a suppressed milk production, leading to agalactia, was also observed. The delay in development was completely reversible and there was no influence on the development of the F2 generation. A special study design was chosen for the conduct of a female fertility study in mice with administration of a ‘safe dose’ determined in a pre-study from mating to implantation, however, only one of the female mice treated with rotigotine became pregnant. This effect is probably also due to the complex influence of dopamine agonists on secretion of sex hormones such as prolactin and the susceptibility of rodents during mating and/or implantation in general.

All these effects are pharmacodynamic effects of the compound. The risk for human is unknown. Rotigotine should not be used during pregnancy. A decreased milk production, inhibition of lactation

is expected. Studies in rats have shown that rotigotine and/or its metabolite(s) is excreted in breast milk. In the absence of human data, breast-feeding should be discontinued.

Studies in juvenile animals were not conducted.

- Local tolerance

An extensive program on local tolerance and sensitization was conducted, including: (1) phototoxicity studies in guinea pigs (patch), (2, 3) studies with administration of clinically relevant patches in guinea pigs and rats, and (4) irritation and sensitization studies in rabbits, guinea pigs and monkeys via transdermal and subcutaneous routes (solution).

In studies on local tolerance or sensitization, rotigotine did not reveal any test substance-specific findings compared to placebo. The human-relevant silicone patches were evaluated in local tolerance studies up to 4 weeks and in sensitization studies (modified Buehler test, photosensitization) and in a study on phototoxicity. All these studies were conducted in comparison to corresponding placebo patches. Overall, effects due to the application and removal procedure of patches were identified after repeated patch administration to the same sites. Therefore, a rotating application scheme of rotigotine patches in human use is strongly recommended. In other studies rotigotine substance was administered in different solvents or suspensions in comparison to standard positive control substances and vehicle controls. In these studies, rotigotine did not reveal any substance-specific sensitization or toxic properties. Rotigotine is not an UV-absorbing compound.

- Other toxicity studies

Dependence:
Three studies to assess the abuse potential of rotigotine, such as cocaine discrimination in rats and monkeys and a study on the effects on i.v. cocaine self-administration in Rhesus monkeys have been conducted. Rotigotine showed potent stimulant-like effects, but these effects are sufficiently different from those of cocaine in primates. The abuse potential of rotigotine in humans is considered to be low. This assumption is supported by data obtained from the broad receptor screen and the specific pharmacokinetic properties related to the patch formulation that does not result in significant plasma level fluctuations.

Interaction studies with L-dopa/carbidopa:
In rats and monkeys, toxic interaction was observed between rotigotine and L-dopa/carbidopa. In monkeys, the number of animals showing restlessness seemed to be increased in animals receiving rotigotine and L-dopa/carbidopa, compared to animals receiving either substance alone. This can be expected, since all these substances are dopamine agonists.

Immunotoxicity:
As assessed by the Plaque Forming Cell assay with sheep red blood cells, there was no effect of rotigotine on the T cell-dependent IgM and IgG antibody response and on spleen weight.

Metabolites:

The phase 1 and phase 2 metabolites were found to be present in all species. Therefore, the potential toxicity of both metabolites has been sufficiently studied with the current non-clinical testing program.

Impurities:
The active active substance contains the following impurities: dethienylethyl rotigotine, depropyl rotigotine, dithienylethyl rotigotine, rotigotine toluenesulfonic acid ester, rotigotine thienylethyl ether, ethyl rotigotine and acetyl rotigotine. No specific preclinical studies have been performed on these impurities. Desthienylethyl rotigotine and despropyl rotigotine are metabolites and therefore qualified. Dithienylethyl rotigotine, rotigotine toluenesulfonic acid ester and rotigotine thienylethyl ether are qualified in the amounts found in the preclinical batches (0.38%, 0.87-0.95%, 0.14-71%, respectively). Ethyl rotigotine and acetyl rotigotine are qualified by the limit of 0.15%.

Toxicological properties of the ingredients:
All ingredients in patches for human use, which were not used in toxicological studies were tested according to guidelines by the manufacturer of the ingredients or are compendial ingredients.
Rotigotine patches produced for clinical use are a matrix-type transdermal system. Neither the adhesives nor its extracts were sensitizing in guinea pigs or produced effects in a bacterial reverse mutation assay or in a cytotoxicity assay with mammalian cell culture. Material extracts were not pyrogenic upon injection into rabbits. No adverse reactions were produced by any extract administered by any route in either species tested in the U.S.P. Class V test.

Ecotoxicity/environmental risk assessment

Assessment of potential risks to the environment is a step-wise, phased procedure. The environmental risk assessment consists of two phases. The first phase (Phase I) assesses the exposure of the environment to the active substance and/or its metabolites. Phase II consists in environmental fate and effects analysis.

Phase I
The risk posed to the environment by the use of rotigotine patch has been initially calculated by the applicant on the basis of the draft 2003 EMEA ERA guideline. With a Predicted Environmental Concentration in surface ($PEC_{SURFACEWATER}$) of 0.0032µg/l, i.e. lower than 0.01µg/l, the applicant claimed an exemption of phase II studies. However, the calculation used a market penetration factor (Fpen) of 0.035%. When, the market penetration factor (Fpen) is defined by default at 1%, the PEC action limit is exceeded. Furthermore the disposal of the patch into waste should be considered as it is expected that it will correspond to a disposal of the test compound into the solid waste. Therefore, a revised ERA according to the draft guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/447/00/draft) was required as well as justification of the estimation of annual consumption of Neupro in the EU should be justified. In addition, a water-sediment-study, studies concerning toxicity to microorganisms, algae, daphnids and fish as well as a bioaccumulation study with fish were requested.

The applicant submitted a revised ERA.

Phase II
Neupro is a transdermal patch. About half the dosage will be discarded in the waste. Based on disease prevalence of about 0.225% and an estimated market share of 10%, the F_{pen} is set at 0.0225%. Based on the reported estimated sales in 2011 in five major EU countries the F_{pen} is also 0.022%. However, based on a maximum market share the $PEC_{surfacewater}$ for the total residue is 10 ng/l. This is the $PEC_{surfacewater}$ to be used for the PEC/PNEC assessment. (PNEC= predicted no-effect concentration)

The EC50 (effective concentration 50%) for activated sludge is 1825 mg/l. The risk to activated sludge is negligible. Rotigotine is not readily biodegradable.

Based on the provided information, the environmental risk assessment could not be completed;
- Information on ecotoxicity, adsorption, and fate in water/sediment systems is lacking,
- The waste stage has not been assessed.

Upon CHMP request, the applicant committed to conduct the following studies on Environmental Risk Assessment (ERA) according to Phase 2 Tier A of the draft EMEA guideline CHMP/SWP/4447/00. Studies will be reported before the end of the third quarter of 2006.
- A soil/sediments adsorption study according to either OECD 106, OECD 121 or OPPTS 835.1110 (the method used will be justified),
- Toxicity to algae (OECD201),
- Daphnia reproduction study (OECD 211)
- Fish early life stage (OECD 210)
- A study on transformation on aquatic sediments (OECD 308) will be performed, if PEC/PNECsurfacewater is >1.

The ERA will be refined according to the results of the above-mentioned studies. The environmental risk related to the waste stage of the product will be addressed in the refined ERA based on leaching rates of the drug from the patches.
If necessary according to the refined Phase 2 Tier A ERA, the Phase 2 Tier B study on bioaccumulation in fish (OECD 305e) will be initiated.

Discussion on the non-clinical aspects

Rotigotine is a D3-selective dopaminergic agonist with affinity for D2-receptors (0.7 and 13,5 nM, respectively; Ki-ratio D2/D3 of 19). Results of preclinical studies demonstrated that rotigotine is effective in animal models of Parkinson disease where it restores locomotor activity. Receptor down-regulation and the development of tolerance as with the chronic use of a D2 receptor agonist, like pergolide is anticipated. Rotigotine is well tolerated in vivo and essentially free of unwanted ancillary pharmacological, electrocardiographic, and behavioral effects. Pharmacokinetics of rotigotine appeared to be approximately linear over the range investigated.

Non-clinical pharmacodynamic interaction studies in MPTP-lesioned animals have not been performed, but non-clinical pharmacology studies in 6-OHDA hemilesioned rats with coadministration of rotigotine and L-DOPA were performed. The co-administration of rotigotine and a dose of L-DOPA that has no effect on its own leads to additive effects on turning behaviour. The coadministration of rotigotine and a dose of L-DOPA known to induce sensitization causes the same degree of rotations and a similar development of sensitization as L-DOPA alone. Overall, rotigotine does not affect the efficacy of L-DOPA, but low doses of L-DOPA may enhance the efficacy of rotigotine or vice versa.

In toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion.

After a single dose of rotigotine, binding to melanin-containing tissues (i.e., eyes) in the pigmented rat and monkey was evident, but was slowly cleared over the 14-day observation period.

Retinal degeneration was observed by transmission microscopy at a dose equivalent to 5.6 times the maximum recommended human dose on a mg/m² basis in a 3-month study in albino rats. The effects were more pronounced in female rats. Additional studies to further evaluate the specific pathology have not been performed. Retinal degeneration was not observed during the routine histopathological evaluation of the eyes in any of the toxicology studies in any species used. The relevance of these findings to humans is not known.

Increased levels of ALT and AST were observed in rats, primarily in females, from an exposure of about 6 times the human exposure. Later data on liver weights and histopathology submitted upon request suggests that the liver should not be considered as a target organ for toxicity.

Rotigotine did not induce gene mutations in the Ames test, but did show effects in the in vitro Mouse Lymphoma Assay with metabolic activation and weaker effects without metabolic activation. This mutagenic effect could be attributed to a clastogenic effect of rotigotine. This effect was not confirmed in vivo in the Mouse Micronucleus Test in the rat Unscheduled DNA Synthesis (UDS) test. Since it ran more or less parallel with a decreased relative total growth of the cells, it may be related to a cytotoxic effect of the compound. Therefore, the relevance of the one positive in vitro mutagenicity test is not known.

Rotigotine did not influence male fertility in rats, but clearly reduced female fertility in rats and mice, because of the effects on prolactin levels which are particularly significant in rodents. Rotigotine was embryotoxic in rats and mice at materno-toxic doses. Rotigotine should not be used during pregnancy. Inhibition of lactation is expected and rotigotine was excreted in breast milk in rats. Breast-feeding should be discontinued.

Based on local tolerance studies, effects due to the application and removal procedure of patches were identified after repeated patch administration to the same sites. Therefore, a rotating application scheme of rotigotine patches in human use is strongly recommended.

The environmental risk assessment could not be completed. The Applicant was asked to further assess the environmental risk and has committed to perform studies on Environmental Risk Assessment (ERA) according to Phase 2 Tier A of the draft guideline on the environmental risk assessment of medicinal products for human use (CHMP/SWP/447/00/draft). The ERA will be refined according to the results of the studies. The Environmental Risk related to the waste stage of the product will be addressed in the refined ERA based on leaching rates of the drug from the patches. If necessary according to the refined Phase 2 Tier A ERA, the Phase 2 Tier B study on bioaccumulation in fish (OECD 305e) will be initiated.

1.4 Clinical aspects

Introduction

Rotigotine is a new chemical substance belonging to the group of non-ergolinic dopamine agonists and developed to treat Parkinson's disease. Due to low bioavailability of this substance via the oral route and suitable physico-chemical properties for transdermal application, rotigotine has been developed for transdermal administration using patch technology.

Initially, an acrylic-based transdermal patch was used. Later a silicone-based formulation with a decreased drug load and higher relative bioavailability was developed. The silicone-based formulation is the final formulation. The major Phase 2b and all Phase 3 trials used the silicone formulation (4.5mg of rotigotine in each $10cm^2$) that is proposed for marketing.

The clinical development program for the silicone patch formulation of rotigotine in early-stage idiopathic Parkinson's disease comprised 7 clinical trials in Phases 2 and 3, of which 6 were placebo-controlled.
The 4 trials in Phase 2a, of which 3 were placebo-controlled, had a maximum exposure to trial medication of 4 weeks. The Phase 2b dose-response trial had maximum treatment duration of 3 months and the exposure to drug in the double-blind portion of the 2 Phase 3 trials was up to 6 months in SP512 and up to 9 months in SP513. Open-label extensions of both Phase 3 trials were ongoing; however, all subjects had been enrolled by the clinical cutoff date of 31 Dec 2003. The uncontrolled Phase 1 trial SP630 was conducted in subjects with early-stage Parkinson's disease with a maximum exposure to trial medication of 5 weeks.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.
The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

It should be noted that in the clinical assessment doses are expressed as initial dose contained in the patches while product information refers to the apparent dose (calculated as difference between initial rotigotine dosage and residual rotigotine amount in the patch after application).
The nominal (apparent dose) patches of 2, 4, 6 and 8 mg of rotigotine /24 hours contain respectively 4.5 mg, 9.0 mg, 13.5 mg and 18.0 mg of rotigotine.

Pharmacokinetics

Rotigotine is a lipophylic dopamine-agonist which is rapidly metabolised after oral application in rodents. In order to avoid the first-pass effect, a rotigotine patch for transdermal application was developed.

Analytical methods were based upon liquid chromatography/mass spectrometry/mass spectrometry (LC-MS/MS).

In 24 clinical studies, the pharmacokinetic profile of the final product, the rotigotine base silicone patch, was studied. Doses varied between 2.25-18 mg in healthy volunteers (11 studies) and between 4.5-54 mg in Parkinson's Disease patients (10 studies). Two studies with 4.5 mg rotigotine doses were performed in patients with renal or hepatic dysfunction, who did not suffer from Parkinson's Disease. One study was carried out in patients with restless-legs syndrome (9 mg). Pharmacokinetic interactions between rotigotine and Parkinson's disease commonly prescribed medications like levodopa, carbidopa, and domperidone and a non-specific CYP substrate and inhibitor cimetidine were studied in healthy volunteers. In all studies, rotigotine patches were applied for 24 hrs.

In several pilot studies, rotigotine was administered intravenously in advanced Parkinson's disease patients, and some plasma-concentration time curves following intravenous administration were reported.

- Absorption and Bioavailability/Bioequivalence

The approximated in vivo absorption of rotigotine after single-dose application was obtained by the Wagner Nelson method. The absorption pattern of drug released by the transdermal system follows apparent zero order kinetics.
Mass balance of radioactive rotigotine has been determined. Only 46.1% of the applied dose has been potentially absorbed (apparent dose) of which 94.6% have been recovered in urine and faeces. The studies confirm that only 46.1% of the dose is released from the patch and absolute bioavailability is 37%.
Two different pilot patch formulations were developed, one based on a silicone formulation and one based on an acrylic formulation. The bioavailability studies demonstrated that the bioavailability of rotigotine was approximately 3 times higher for the silicone patch compared to the acrylic-type patch (based on the ratio of AUCs). Thus, the silicone-based patch was considered to be suitable for further clinical development. Initially, in the patch manufacturing process rotigotine free base was liberated from its hydrochloride salt. Once the free base became available in crystalline form the manufacturing method was modified by replacing the hydrochloride salt with rotogotine free base as starting material . Silicone patches obtained by both methods have shown to be bioequivalent.
The equivalence of 6 different application sites (abdomen, flank, upper arm, shoulder, thigh, and hip) in subjects with early-stage, idiopathic Parkinson's disease has been studied but not demonstrated. The 90% CI of the ratio between different application sites ranged from 0.72-1.41%. However they were sufficiently similar so that this can support rotation of application site, given that the effect of anti-parkinson agents is not strictly related to constant high levels but tolerate some fluctuation as long as the levels do not fall below a minimum.
Normalisation of plasma concentrations and parameters for the apparent dose has been questioned but the applicant states that it has not been used for studies involving pharmacokinetic comparisons.

Apparent dose
Another method of assessment of individual bio-availability was estimation of apparent dose. Apparent dose was calculated as difference between initial rotigotine dosage and residual rotigotine amount in the patch after application. The actual dose was 0.45 mg per square centimeter rotigotine patch in all strengths.

- Distribution

In vitro, rotigotine binds to plasma proteins to an extent of 91.6±1.1%, mainly mediated by serum albumin (81%). These in vitro data obtained at supra-therapeutic concentrations were confirmed in 2 Phase 1 trials in vivo, which showed mean plasma protein binding of 89 to 92%.
The large volume of distribution at steady-state of 84 l/kg indicates wide distribution of rotigotine into tissues. This was supported by pre-clinical data showing a rapid and wide distribution throughout tissues in rats and a rapid and wide distribution in the brain of monkeys.

- Metabolism and Elimination

Rotigotine is extensively metabolised. Urine excretion of unconjugated rotigotine is negligible.
In vitro investigations in human liver microsomes showed that rotigotine is primarily converted by dealkylation to a despropyl- or desthienylethyl-metabolite or by monohydroxylation. CYP2C19 is the major CYP450 isoform involved in the metabolism of rotigotine. Despropyl and desthienylethyl phase 1 metabolites undergo further conjugation with either sulphate or glucuronic acid. The rotigotine-conjugates are not biological active.

With a clearance of 630 l/h, rotigotine can be regarded as a high clearance drug. The plasma terminal half-life after transdermal application is 5 to 7 hours.

After intravenous application of radiolabelled rotigotine, approximately 71% of the radioactivity was eliminated in urine and 23% in faeces. Rotigotine and its metabolites are mainly excreted in urine (about 70 % of the total dose), and to lesser extent into bile and faeces. There were no signs for enterohepatic cycling of the conjugated metabolites.

- Dose proportionality and time dependencies

Dose proportionality was shown with PK parameters Ctrough, AUC, and Cmax of rotigotine up to an applied dose of 18.0mg/day for healthy subjects as well as subjects with early-stage Parkinson's disease.

The metabolic pattern of rotigotine does not indicate that this drug is prone to self-induced metabolism. Furthermore, experience drawn from pharmacokinetic data from phase 2 and phase 3 clinical trials does not support the hypothesis of time dependency. The mean plasma concentration levels measured at different dose levels indicate dose proportionality and the steady-state concentrations remained stable during the 6-month maintenance period.

- Inter-variability

The inter-individual variability in rotigotine exposure after patch application was significant. Inter-individual variability of the rotigotine AUC's was estimated between 40-70%. Variability in rotigotine levels was only partly explained by body weight. Renal and hepatic functions were no significant covariates in population PK models.

- Special populations

Impaired renal function
Plasma concentration-time profiles of unconjugated rotigotine were similar in subjects with different stages of renal impairment and healthy subjects.

Plasma concentrations of total rotigotine were higher in subjects with severe renal impairment compared to healthy subjects. Compared with healthy subjects, plasma levels of total despropyl- and desthienylethyl- metabolites determined 23.5 hours after patch application increased in subjects with severe renal impairment by 8.4- and 5.9-fold, respectively. Similar data were observed in end-stage renal impairment patients requiring dialysis.

Based on the data for the exposure to the active compound (unconjugated rotigotine) and since the metabolites have been demonstrated to be ineffective both in efficacy and safety terms, no dose adjustment is necessary in subjects with different stages of renal impairment. However, rotigotine dose adjustments seemed to be necessary in patients with acute onset of renal dysfunction. Rotigotine was not removed from the body by extracorporeal or haemo-dialysis.

Impaired hepatic function
Results show that mean plasma concentration-time curves were similar in hepatic impaired and healthy subjects. The statistical analysis of primary pharmacokinetic parameters did not show significant differences in the exposure to unconjugated rotigotine in both subject groups.

Plasma levels of total rotigotine were slightly higher in subjects with hepatic impairment. There was no relevant difference in the urinary excretion of unconjugated rotigotine, whereas the amount of total rotigotine was higher in subjects with hepatic impairment. Excretion of total despropyl-and desthienylethyl rotigotine was higher in hepatic impaired subjects compared with healthy subjects.

Based on these pharmacokinetic data, no rotigotine dose adjustment is necessary for subjects with moderate hepatic impairment. However no data concerning patients with severe hepatic impairment has been provided. Therefore, appropriate statements in the SmPC have been included.

Gender, race, weight and age
Similar rotigotine plasma concentrations and pharmacokinetic parameters AUCss and Cmax,ss were observed in female and male subjects with Parkinson's disease treated with the highest proposed therapeutic dose in trial (18.0mg).
The pharmacokinetic profile of rotigotine was characterized in Black compared to Caucasian subjects as well as in Japanese subjects compared to Caucasian subjects. No interethnic differences were observed in the pharmacokinetic profile of rotigotine in Japanese, Black, and Caucasian subjects, following body weight normalisation.

The comparison of plasma concentration data determined in 2 Phase 3 trials addressed the possible influence of age on the pharmacokinetics of rotigotine. No differences in plasma concentration were observed between patients <65 years and >65 years with early-stage Parkinson's disease.
However, apparent dose was significantly lower in patients (±33%) in comparison with healthy subjects (±50%). These data might indicate that both absorption and metabolism/excretion were diminished in the patients group. The applicant explained that it is known from the literature that absorption through the skin and renal excretion is diminishes with age. The lower absorption in elderly is "compensated" by lower excretion rate, and rotigotine exposure was therefore similar in older patients and younger healthy volunteers.

- Pharmacokinetic interaction studies

In vitro, several CYP isoforms are involved in the biotransformation of rotigotine in human liver, including CYP 2C19. The data indicate a low in vivo drug interaction potential with respect to CYP mediated drug metabolism. Rotigotine was not a substrate of P-glycoprotein in vitro and did not interfere with the drug transport of digoxin.

In vitro data support a limited package of in vivo drug-drug interaction studies. Therefore, the applicant performed interaction studies with cimetidine (a non-specific CYP 450 isoform substrate and inhibitor), domperidone because of its use in nausea and vomiting induced by rotigotine and with carbidopa, levodopa, because of its concomitant use. Studies demonstrated no relevant change in the pharmacokinetics of rotigotine in the presence of these drugs.

Since several sulfotransferases and only two UDP-glucuronosyltransferases (UGT1A9 and UGT2B15) are involved in the metabolism and maximum concentrations of rotigotine are well below the saturating concentrations for these enzymes, it seems unlikely that the co-administration of other drugs metabolized by conjugation might have an influence on the plasma concentration of rotigotine because other enzymes can take over the metabolism. Low affinity of rotigotine to these enzymes precludes in principle the possibility of rotigotine inhibiting other drugs metabolism.

Pharmacodynamics

Rotigotine was characterized as a *typical* dopamine agonist in non-clinical studies. There was no attempt to further characterize its pharmacology in human studies.

Rotigotine inhibits prolactin secretion in the range of what is expected for a dopamine agonist.
The effects of rotigotine treatment on prolactin levels were determined in a healthy subjects trial (14 day treatment with 4.5mg daily) as well as in phase 3 trial SP512. In healthy subject, prolactin levels decreased after application of the first rotigotine patch from 13.7ng/mL to 7.2ng/mL. Mean concentration remained at a low level until application of the last patch. In trial SP512, for subjects receiving placebo, the mean prolactin serum levels were between 6.4 and 7.7ng/mL and decreased to between 4.8 and 5.4ng/mL during the maintenance period after application of the 13.5mg patch.

Two clinical trials were conducted in healthy subjects to address specific safety issues regarding skin tolerability of the rotigotine transdermal patch. These trials are described in detail in the safety section.

Clinical efficacy

The Unified Parkinson Disease Rating Scale (UPDRS) is the most common and most frequently used assessment scale for evaluating treatment responses in Parkinson's Disease. For early Parkinson's Disease, the part II (activity of daily life) and part III (motor-examination) of the UPDRS is accepted in the CHMP guideline as primary efficacy variable in early Parkinson's Disease.

The Unified Parkinson Disease Rating Scale (UPDRS) is a compilation of various Parkinson assessment scales, all measuring specific aspects of Parkinson's Disease. The scale has five sections: Part I Mentation, behaviour and mood, measuring the psychological aspects of the disease and/or treatment (Questions 1-4), Part II Activities of daily life (Questions 5-17), Part III Motor examination mainly scoring clinical signs and symptoms (question 18-31), Part IV Complications of therapy (Dyskinesias Questions 32-35, Clinical fluctuations Questions 36-39, Other complications Questions 40-42) and Part V the Modified Hoehn Yahr staging (Stage 0-5).

Question in part I-IV are scored on a 0-4 point rating scale with the exception of some questions in part IV which are dichotomous (complication present/not present). The Modified Hoehn Yahr is primary a staging scale and less sensitive to change.

- Dose response studies

The table below summarizes the dose-finding studies that were conducted in rotigotine's clinical development. The most robust of these studies is study 506, that was a large double-blind, placebo controlled study. Main inclusion and exclusion criteria were similar to those of the phase 3 trials (see next section).

Completed, Phase 2 Dose-Ranging Trials of Rotigotine in Early-Stage, Idiopathic Parkinson's Disease

Trial Number/Clinical Development Phase/Trial Design	# Subjects Receiving Rotigotine	# Subjects Receiving Placebo	Maximum Treatment Duration
SP534 (Part 1)/Phase 2a/SC, DB, PC, parallel-group, fixed-dose, dose-ranging in early-stage, Parkinson's disease; cohorts of 9.0mg and 13.5mg daily doses.	10	2	28 days
SP534 (Part 2)/Phase 2a/ SC, DB, PC, parallel-group, dose-titration, dose-ranging in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	10	2	28 days
SP540/Phase 2a/MC, SB[a], dose-titration, efficacy, safety in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	31	0	28 days
SP535/Phase 2a/SC, DB, PC, dose-escalation, safety and tolerability in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	8	2	28 days
SP506/Phase 2b/MC, DB, PC, parallel-group, dose-ranging in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	253[b]	76[b]	3 months
Total	312	82	-

DB=double-blind, MC=multicenter, PC=placebo-controlled, SB=single-blind, SC=single center.

a The protocol for SP540 refers to the trial as a single-blind trial, however, the subjects were blinded only to dose; subjects were aware that they were receiving rotigotine.

b In the SP506 CTR, 248 subjects were included in the rotigotine treatment group and 81 in the placebo group for "as treated" analyses. Upon review of the data for pooling, 5 subjects from SP506 were reassigned from placebo to rotigotine to more accurately reflect the subjects' treatment.

In study 506 the primary efficacy variable was the change in Unified Parkinson's Disease Rating Scale (UPDRS) [Parts II+III] score from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77). Results are shown in the table below. The safety profile of rotigotine was determined by the analysis of the frequency and severity of adverse events (AE) and changes in vital signs, electrocardiograms (ECG), and clinical laboratory values recorded over the course of the trial.

Change from Baseline to End of Treatment (EOT) in UPDRS Parts II+III Scores by Treatment Group in SP506 (FAS, Randomized)

		Rotigotine daily dose			
UPDRS Parts II+III	**Placebo (N=62)**	**4.5mg (N=65)**	**9.0mg (N=60)**	**13.5mg (N=61)**	**18.0mg (N=68)**
Baseline (Visit 2) mean (SD)	28.02 (11.114)	28.48 (12.050)	28.52 (11.205)	27.57 (13.462)	27.13 (13.405)
EOT (Visit 6) mean (SD)	26.63 (13.491)	24.98 (11.789)	24.05 (11.528)	21.33 (13.328)	20.84 (11.511)
Mean change from baseline (SD)	-1.39 (7.904)	-3.49 (7.233)	-4.47 (6.808)	-6.25 (6.777)	-6.29 (7.825)
ANCOVA comparison I[a]					
Effect estimate		-2.148	-3.123	-4.909	-5.035
p-value		0.0393	0.0063	<0.0001	<0.0001
[95% CI]		[-4.544, 0.248]	[-5.571, -0.675]	[-7.341, -2.477]	[-7.406, -2.665]

ANCOVA = Analysis of covariance, FAS = Full analysis set, UPDRS = Unified Parkinson's disease rating scale

a Model included treatment group as a factor, country as a stratification factor, and baseline value as a covariate; a 1-sided p-value was obtained. Each significance test was performed at the 2.5% level.

In this trial rotigotine was efficacious in treating the manifestations of Parkinson's disease as measured by UPDRS Parts II+III scores. At the end of treatment, each of the rotigotine groups had numerically better improvement compared to the placebo group. Statistically significant differences in change from baseline in the UPDRS Parts II+III scores were observed between the rotigotine 9.0mg/day, 13.5mg/day, and 18.0mg/day groups and placebo (effect estimates were -3.123 for 9.0mg/day, -4.909 for 13.5mg/day, and -5.035 for 18.0mg/day for the full analysis set).
In general, the proportions of subjects showing ≥20% and ≥30% decreases in the UPDRS (Parts II+III) increased with increasing rotigotine dose up to 13.5mg/day. Responder rates were similar in the rotigotine 13.5mg/day and 18.0mg/day dose groups. For the ≥20% responder group, the proportion of responders was 57% and 53% for the 13.5mg/day and 18.0mg/day dose groups, respectively. The corresponding proportions for the ≥30% responder group were 41% and 44%.

This main dose-finding study confirmed the suggestions of the early phase 2 trials:

- dose titration to target dose makes dopaminergic side-effects manageable;
- rotigotine is efficacious in controlling PD symptoms in the range of doses from 4.5 mg/d to 18 mg/d;
- there is a dose-response effect that plateaus at 13.5 mg;
- the 18 mg/d is not distinguishable from the 13.5 mg/d;
- the effect size considering UPDRS part III which was not the primary endpoint (this was part II + III) but is considered here because it is a more frequently used in routine practice is clinically relevant for doses ≥ 9 mg/d;
- secondary clinical outcomes were consistent with the primary endpoint.

- Main studies: Studies SP512 and SP513

Following study SP506 results, 13.5mg/day and 18.0mg/day were investigated in the pivotal trials. In order to determine its efficacy and safety as an anti-Parkinsonian agent, rotigotine was evaluated in 2 Phase 3 trials involving subjects with early-stage, idiopathic Parkinson's disease. Trials SP512 (Part I) and SP513 (Part I) had virtually identical trial designs and endpoints. Their designs are summarised below.

Summary study design of main studies

Study	**Study SP512**	**Study SP513**
Design	Randomised, multicenter (47), double-blind, placebo-controlled, parallel group design	Randomised, multicenter (81), double-blind, placebo-controlled, active controlled, parallel group design
Main in-/exclusion criteria	Patients with Early Parkinson's Disease; Hoehn & Yahr stage ≤ 3; MMSE ≥ 24 (25); Stable on selegiline, anticholinergic agents or amandatine; No dopamine-agonists within 28 days of baseline; No L-dopa+ within 28 days of baseline, No L-dopa+ > 6 months in past; No skin hypersensitivity to adhesive transdermals; No severe co-morbidity.	
Study arms	Placebo CDS Rotigotine CDS	Placebo capsules TID / Placebo CDS Placebo capsules /Rotigotine CDS Ropinirole TID / Placebo CDS
Study periods	Run-in ≈ 28 days Titration [a, b] 21 (+9) days Maintenance [c] 168 (+7) days De-escalation up to 4 days Safety fu 28 (+7) days	Run-in ≈ 28 days Titration [a, b] ≤ 91(+39) days Maintenance [c] 168 (+7) days De-escalation up to 12 days Safety fu 28 (+7) days
Subjects will receive either	Each subject was titrated to the optimal or maximal dose allowed: Placebo patch Rotigotine 4.5, 9.0, 13.5 mg	 Placebo Rotigotine 4.5 , 9.0, 13.5 or 18 mg[d] Ropinirole 0.75, 1.5, 2.25, 3.0, 4.5, 6.0, 7.5, 9.0, 12, 15, 18, 21, 24 mg/day
Efficacy		
Primary variables	EU: Responders defined as a subject with a ≥ 20% improvement in UPDRS II+III score from baseline. USA: change in UPDRS-II-III score from baseline.	
Main secondary variables	Change in UPDRS score II, III, CGI; Change in Hoehn-Yahr stage; QoL by EQ-5D; (Epworth scale score)[e]	
Safety	Adverse events, vital signs, QT-time, viral signs, orthostatic hypertension, clinical laboratory values .	

CDS: continuous delivery system

Notes
[a] number in parentheses indicates variation in time window allowed.
[b] Each subject was titrated to the optimal or maximal dose allowed.
[c] During titration back titration was allowed once. During the maintenance period back titration was not allowed.
[d] Rotigotine 4.5 mg has a patch size of 10 cm^2, Rotigotine 9 mg = patch size of 20 cm^2, Rotigotine 13.5 mg = patch size of 30 cm^2, Rotigotine 18 mg = 2 patches of 20 cm^2 each.
[e] ( ) = not in study SP513

METHODS

Study Participants

Patients were included in these trials if they had been diagnosed with idiopathic PD of ≤5 years in duration, had a Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Part III) of ≥10 at baseline (Visit 2), had a Hoehn & Yahr stage ≤III; had at least 2 or more of the following cardinal signs: bradykinesia, resting tremor, rigidity, postural instability; and were without any other known or suspected cause of Parkinsonism.

The following anti-Parkinson's agents were allowed provided the dose was kept stable and the agents were used for at least 28 days prior baseline: MAO-B inhibitors, anticholinergic agents, NMDA (N-methyl-D-Aspartate)–antagonists. CNS active agents allowed were: sedatives, anti-depressants, hypnotics and anxiolytics, again provided the dose was kept stable and the agents were used for at least 28 days prior baseline.

The anti-emetics allowed were restricted to non-dopamine-agonists.

Not allowed were dopamine-agonist /-antagonist, L-dopa, COMT, MAO-A inhibitors and other agents interfering with dopamine dynamics. Basically these concerned concurrent medication, among which carbidopa/levodopa, dopamine-agonists, MAO-inhibitors, anti-dopaminergic antiemetics. When subjects required these treatments they were discontinued from the trial.

Treatments

After a run-in period of about 28 days, patients entered a dose escalation phase where they were titrated to the optimal or maximal dose allowed. The optimal dose was defined as the dose that gave the maximal reduction in Parkinson's disease symptoms without intolerable side effects. The optimal dose was determined following discussion of patient and investigator. During the dose escalation phase back titration was allowed once. The duration of the dose escalation period differed considerable between studies SP512 and SP513 due to the much slower titration schedule of subjects receiving ropinirole in study SP513.

After the optimal dose was established the patient entered the maintenance phase lasting 24 weeks. The dose was kept constant and if back-titration occurred during this period a subject was withdrawn. At the end of the study a 4 (study SP512) to 12 day (study SP513) blinded de-escalation followed. Finally there was an open label off study drug follow-up of 4 weeks for those patients not entering the open label extension study.

The patches were applied for a period of 24 hours. Preferably the patches were applied to the upper or lower abdomen (above the umbilicus) but thigh, hip, flank, shoulder, and/or upper arm formed an alternative. The skin should be healthy, cleaned and dry. The application site of the patches was rotated on a daily basis (i.e. to contra-lateral sides of the upper abdomen). A period of 14 days was left between one and the next application to the same area. New patches should be applied at the same time daily and immediately after the previous day's patches have been removed.

During the titration phase, dose could be increased after one week of the lower dose. During the de-escalation phase, the daily dose of rotigotine was decreases by 4.5 mg every two days whereas the subjects on ropinirole were down-titrated from 24 to 18 to 12 to 7.5 to 4.5 to 5 to 2.25 and to 0.75 mg/daily every two days.

Objectives

To evaluate efficacy, safety and tolerability of rotigotine continuous delivery system (CDS) in early Parkinson's Disease compared to placebo and, in study SP513, ropinirole.

Outcomes/endpoints

The primary efficacy assessment was based upon the UPDRS-II-III score. The approach to defined different primary endpoint for US and EU was done a priori. Responder rates were used as the primary outcome variable in the EU and mean change from baseline in UPDRS parts II and III was used as the primary outcome in the US. Secondary efficacy variables were the relative and absolute change in UPDRS-II-III score over time, the separate UPDRS-II and UPDRS-III scores and the AUC of UPDRS-II-III in the maintenance phase. See above summary table.

Sample size

Study SP512:
An absolute difference in response rates of 20% was judged as being clinically meaningful. Based on study SP406 the response rates for placebo was assumed to be 30% maximally and 50% for rotigotine CDS minimally. A sample size of 160 in the rotigotine arms and 80 subjects in the placebo arm (2:1 randomization) allowed detection of a statistically significant difference in response rates between the two groups, with a power of at least 80% using a two sided 5% Fisher's exact test. It was estimated that 300 subjects had to be enrolled in order to have 250 subjects randomised.

Study SP513:
The sample size was determined by the active comparison i.e. rotigotine versus ropinirole, with a non-inferiority margin of 15% and equal proportion of responders in both active study arms.
For the comparison to placebo, assuming a responder rate of 30% for placebo and 50% for rotigotine CDS, 90 subject in the placebo arm were be sufficient to show a statistical significance (two-sided fisher's exact test with a 5%), with a power of 85%.
It was estimated that 540 subjects had to be enrolled in order to have 470 subjects randomised.

Randomisation

Subjects were randomised centrally by an interactive voice response system. In both studies subjects were randomised in a 2:1 ratio (active treatment : placebo).

Blinding (masking)

All placebo and rotigotine patches and their accompanying packaging were identical in appearance. The same holds for ropinirole capsules /placebo capsules in study SP513. For study SP 513 a double dummy technique was needed to maintain the blinding. For blinding purposes, ropinirole tablets were encapsulated into hard gelatine capsules.

The de-escalation phase was blind as well.

Statistical methods

No interim analyses were intended.

Study SP512
The primary analysis was based on the Full Analysis Set (all randomized patients having a baseline and at least one post baseline measurement for the primary variable). The Fisher's exact test was used to test the null-hypothesis of no difference in proportion of responders between placebo and rotigotine versus the alternative hypothesis that the proportion responders differ. All analysis of the primary and secondary variables was based upon the last observation carried forward. The two-sided significance test for the confirmatory analysis was performed at the 5% level. For all other situations, testing was only performed in an exploratory manner by presenting p-values and/or 95%-confidence intervals.

Study SP513
The statistical methods described above for study SP512 also hold for study SP513. However, based on the trial design (three arm parallel group), different null hypothesis was tested in a pre-assigned order (closed test principle). The test procedure starts with a two-sided (α=5%) test between rotigotine and placebo. In case of rejection, it proceeds to a one-sided full level (α=2.5%) non-inferiority test (with non-inferiority margin of 15%) between rotigotine and ropinirole. In case of rejection, and if the lower confidence limit for the treatment effect lies above zero, then there is evidence of superiority and a two-sided level α=5% test could be performed.

RESULTS

Participant flow

The number of patients recruited, randomised and completing study SP512/SP513 are presented in the following table.

Patient flow /Numbers analysed

STUDIES	**SP512**		**SP513**		
$n_{recruited}$	302		610		
	Placebo	Rotigotine	Placebo	Rotigotine	Ropinirole
$n_{randomised}$	96	181	118	215	228
$n_{non\text{-}completers}$	15 (16%)	39 (22%)	34 (29%)	64 (30%)	54 (24%)
Due to[A]					
Lack of efficacy	6 (6.3%)	12 (6.6%)	22 (19%)	14 (7%)	8 (4%)
Adverse events	6 (6.3%)	24 (13.4%)	6 (5%)	37 (17%)	29 (13%)
Other reasons[B]	6 (6.3%)	8 (4.4%)	11 (9%)	22 (10%)	22 (10%)
n In safety data set **(SS)**	96 (100%)	180 (99%)	118 (100%)	215 (100%)	228 (100%)
n in full analyses dataset **(FAS)**	96 (100%)	181(98%)	117 (99%)	213 (99%)	227 (99%)
$n_{in\ per\ protocol\ data\ set}$ **(PPS)**	80 (83%)	148 (82%)	77 (65%)	145 (67%)	157 (69%)

[A] Subjects could drop out for more than one reason.
[B] Other reason included: withdraw consent, lost to follow-up or still other reasons.

Baseline data

STUDY SP512

The average age of randomized subjects was 63 years old; 55% of the subjects were <65 years old, 31% were 65-74 year old, and 14% were ≥75 years old. The majority of subjects were male (60% in the placebo group, 68% in the rotigotine group), and nearly all subjects (96%) were white. Compared with rotigotine-treated subjects, a greater proportion of placebo-treated subjects were >75 years old (11% versus 21%). Otherwise, there were no important differences in demographics between treatment groups in the efficacy dataset or the per protocol data set at baseline.

In the safety set at baseline, the majority of subjects (57%) had a CGI score of 3 indicating mild illness. Sixty-five percent of subjects had a UPDRS II score of ≤9 (the maximum [worst] UPDRS II score is 52), 81% had a UPDRS III score of ≤29 (the maximum [worst] UPDRS III score is 108), and 54% of all subjects had a UPDRS II+III score of ≤29. The baseline characteristics are in line with expectations for an early PD population. Patients were mostly enrolled at stage 2 H&Y and there were no important imbalances between placebo and rotigotine groups. Furthermore despite the relative liberal inclusion criteria in what concerns previous dopaminergic therapy the actually enrolled patients were, in practical terms, never exposed to such therapies and therefore that exposition cannot be thought as a source of bias.

STUDY 513

Overall, the average age of randomized subjects in the Safety data set was 61.1 years old; 58% of the subjects were <65 years old, 35% were 65-74 years old, and 6% were ≥75 years old. The majority of subjects were male (placebo: 58%, rotigotine: 55%, ropinirole: 60%) and nearly all subjects (96% overall) were white. There were no important differences in demographics between treatment groups in the per protocol data set at baseline.

At baseline for the Safety data set, the majority of subjects (51%) had a CGI score of 3 indicating mild illness. The majority (45%) of all subjects had a UPDRS II+III score of 15-29, and 36% of all subjects had a UPDRS II+III score of 30-44. There were no notable differences in baseline characteristics between treatment groups in the Safety data set or the per protocol data set at baseline.

Outcomes and estimation

Results for both studies are summarised in the tables below:

Efficacy: Primary Outcome EU: RESPONDERS

STUDIES	**SP512**		**SP513**		
RESPONDERS [A]	**Placebo** n=96	**Rotigotine** n=177	**Placebo** n=96	**Rotigotine** n=213	**Ropinirole** n=227
20% improvement	**18 (19%)**	**84 (48%)**	**35 (30%)**	**110 (52%)**	**155 (70%)**
$CI_{95\%\ difference\ vs.\ placebo}$	**28.8% 18.0% <> 39.4%**			**21.7% 11.1% <> 32.4%**	**38.4% 28.1% <> 48.6%**
$CI_{95\%\ difference\ vs.\ Ropinirole}$	-			**-16.6% -25.7% <> -7.6%**	
25% improvement	15 (16%)	77 (48%)	32 (27%)	102 (48%)	144 (63%)
$CI_{95\%\ difference\ vs.\ placebo}$	27.9% 17.6% <> 38.2%			20.5% 10.0% <> 31.0%	36.1% 25.9% <> 46.3%
$CI_{95\%\ difference\ vs.\ Ropinirole}$	-			-15.5% -24.7% <> -6.4%	
30% improvement	12 (13%)	66 (37%)	28 (24%)	90 (42%)	134 (59%)
$CI_{95\%\ difference\ vs.\ placebo}$	24.8% 15.1% <> 34.5%			18.3% 8.1% <> 28.5%	35.1% 25.1% <> 45.1%
$CI_{95\%\ difference\ vs.\ Ropinirole}$	-			-16.8 -26.0 <> -7.6%	

[A]Full analysis data set, last observation carried forward .

Efficacy: Primary Outcome USA: UPDRS-II-III

STUDIES	**SP512**		**SP513**		
	Placebo	**Rotigotine**	**Placebo**	**Rotigotine**	**Ropinirole**
n	96	177	117	213	227
UPDRS II/III score[A]					
Baseline	30.0 (10.7)	29.9 (12.2)	31.3 (12.6)	33. (12.6)	32.2 (12.4)
Change begin maintenance	-1.5	-6.2	-7.5	-11.1	-13.2
Change end of maintenance	1.5	-3.8	-3.3	-8.3	-12.9
Ancova[B]					
End of maintenance	1.31	-3.98	-2.33	-6.83	-10.78
$CI_{95\%\ difference\ vs.\ placebo}$		-5.28 -7.6 <> -2.96		-4.49 -6.64 <>-2.35	-8.45 -10.57 <>-6.34
$CI_{95\%\ difference\ vs.\ Ropinirole}$				3.96 2.18 <> 5.73	

[A]Full analysis data set [B]Ancova: Treatment effect results adjusted for geographic region and Baseline UPDRS

Efficacy: Secondary Outcome variables

STUDIES	**SP512**		**SP513**		
	Placebo	**Rotigotine**	**Placebo**	**Rotigotine**	**Ropinirole**
N	96	177	117	213	227
UPDRS-II score[A]					
Baseline	8.7	8.3	8.7	9.3	9.1
Begin maintenance	-0.8	-1.4	-1.4	-2.9	-3.4
End of maintenance	1.0	-0.3	-0.2	-2.0	-3.0
UPDRS-III score[A, C]					
Baseline	21.3	21.6	22.0	23.8	23.2
Begin maintenance	-2.1	-4.9	-4.8	-7.5	-8.8
End of maintenance	0.5	-3.5	-2.1	-5.3	-8.0
GGI-severity[B]	Baseline → End maintenance		Baseline → End maintenance		
Normal	0% → 0%	2% → 1%	2% → 1%	2% → 4%	2% → 6%

Efficacy: Secondary Outcome variables

STUDIES	SP512		SP513		
	Placebo	**Rotigotine**	**Placebo**	**Rotigotine**	**Ropinirole**
N	96	177	117	213	227
Borderline ill	14% → 6%	17% → 16%	14% → 18%	13% → 23%	11% → 38%
Mildly ill	63% → 66%	58% → 65%	47% → 54%	49% → 52%	54% → 43%
Moderately ill	22% → 26%	22% → 16%	32% → 25%	33% → 20%	30% → 39%
Markedly ill	1% → 2%	1% → 1%	3% → 1%	3% → 2%	3% → 4%
CGI-change[B]	End of maintenance		End of maintenance		
Very much improved	1%	2%	8%	10%	18%
Much improved	7%	17%	16%	32%	42%
Minimally improved	21%	38%	24%	30%	23%
No change	40%	23%	28%	17%	13%
Minimally worse	28%	18%	20%	11%	4%
Much worse	1%	1%	2%	1%	0%
Very much worse	1%	1%	0%	0%	0%
EU-QoL 5D[B]	End of maintenance		End of maintenance		
No problems walking about	49%	56%	35%	41%	51%
No problems with self-care	71%	73%	44%	51%	60%
No problems performing usual activities	43%	53%	25%	37%	47%
No Pain or Discomfort	45%	56%	27%	37%	44%
No Anxiety or Depression	67%	68%	37%	44%	46%

[A] Full analysis data set ,
[B] Safety data set

STUDY SP512

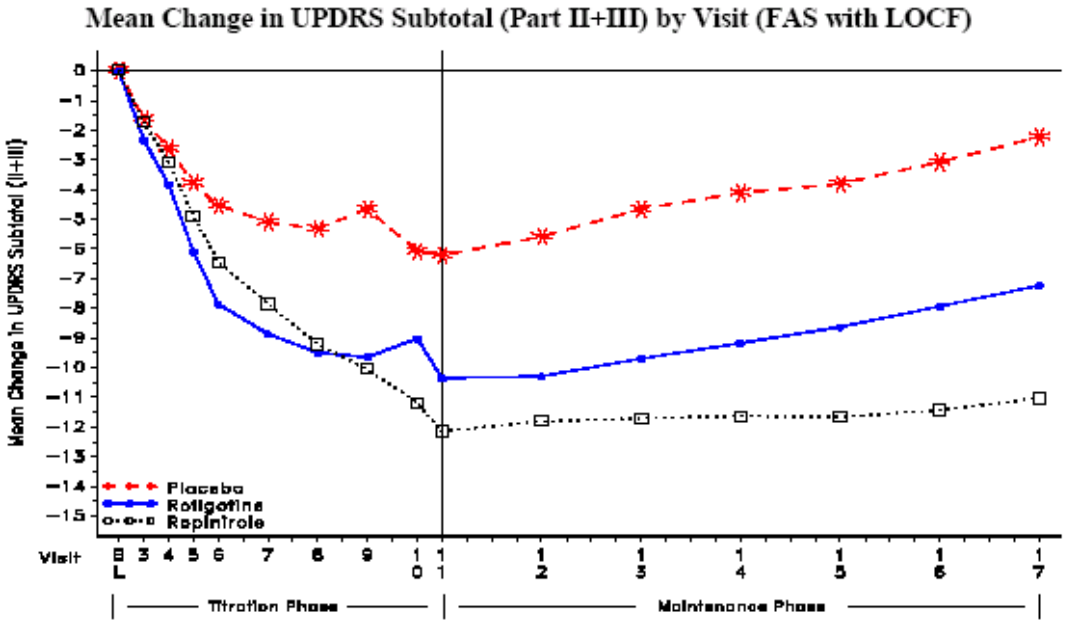
Rotigotine improved the absolute UPDRS (Parts II+III) subtotal score at the end of treatment of approximately -4 points, whereas the equivalent score in placebo-treated subjects indicated deterioration (+1.3 points). These end of treatment scores are highly statistically significantly different from each other ($p<0.0001$).

Rotigotine resulted in a higher proportion of responders at the end of treatment compared with placebo for all of the pre-defined responder groups (ie, for 20%, 25%, and 30% improvements in the UPDRS (Parts II+III) subtotal scores). For all groups, these end of treatment responder proportions are highly statistically significantly different from each other ($p<0.0001$).

The secondary endpoints were consistent with the beneficial effect of rotigotine seen in the primary endpoints. In particular improvement in UPDRS part III was about 3p.

STUDY SP513

The adjusted mean change from baseline in absolute UPDRS (Parts II+III) subtotal score to the end of treatment was -6.83 points (indicating improvement) for rotigotine-treated subjects. Ropinirole- and placebo-treated subjects experienced improvements of -10.78 points and -2.33 points, respectively.



FAS=full analysis set, LOCF=last observation carried forward, UPDRS=Unified Parkinson's Disease Rating Scale

The end of treatment responder proportions (20% cut point) for rotigotine and placebo are statistically significantly different from each other ($p<0.0001$). The difference between rotigotine and ropinirole did not show non-inferiority. The results obtained for each of the other analysis populations (PPS with LOCF and End of Maintenance Visit Completers) were consistent with the results of the primary analysis.

The secondary endpoints analysis goes in line with the main analysis. The effect size in UPDRS part III (referred to baseline) was 5.3 p to rotigotine and 8.0p to ropinirole.

This trial failed to prove the non-inferiority of rotigotine to ropinirole. In fact ropinirole was superior. This finding is consistent across all analysis. If study SP513 had been a two arm non-inferiority study with ropinirole and rotigotine as active treatments, non-inferiority would not have been shown (20% responders under ropinirole 70% under rotigotine 52%, difference 16.6 %; CI 95% [-25.7%; -7.6%]). See discussion on clinical efficacy.

- Clinical studies in special populations

Studies in advanced Parkinson's Disease were ongoing at the time of the assessment of the application in early Parkinson disease.

- Ancillary analyses

Comparison of results by rotigotine maintenance dose
Few subjects received 4.5mg/day or 9.0mg/day as their rotigotine maintenance dose in either SP512 or SP513. The available data for these doses suggest, however, that 9.0mg/day rotigotine may be an effective dose in some patients.

Comparison of UPDRS Subtotal (Parts II+III) Mean Change from Baseline by Rotigotine Maintenance Dose (FAS with LOCF)

Dose (mg/day)	SP512 (Part I)		SP513 (Part I)	
	N	UPDRS II+III Change from Baseline	N	UPDRS II+III Change from Baseline
Placebo	96	1.5	117	-2.2
Rotigotine Overall	177	-3.8	213	-7.2
4.5	4	-2.0	2	-3.5
9.0	11	-6.6	6	-14.0
13.5	162	-3.6	7	-4.9
18.0	0	This dose was not studied.	198	-7.2

FAS = Full analysis set, LOCF = Last observation carried forward, UPDRS = Unified Parkinson's disease rating scale

The comparative analysis of studies SP512 and SP513 show that the effect size of rotigotine benefit is consistent although somewhat smaller in the study 512 that had a maximum dose lower than the SP513. This suggests that the dose-response may not plateau within the dose-range studied in these studies.

- Supportive studies

The long-term efficacy of rotigotine was being evaluated in two, open-label extension trials (SP512, Part II; SP513, Part II). As for the Part I portions of these trials, the trial designs for SP512 and SP513 Part II were nearly identical.

All subjects began treatment with rotigotine at a dose of 4.5mg/day after completing the DB deescalation. Because the rotigotine dose may have been up-titrated every 7 ± 3 days by 4.5mg (10cm^2) increments to a maximum dose of 13.5mg/day (during the 1st year of open-label treatment), the maximum length of the Titration Phase was 30 days.

The data generated by the open-label long term extensions (see below) suggested that efficacy is maintained in a relevant proportion of individual up to 12 month and possibly 18 months of monotherapy but again suggested lesser efficacy than ropinirole.

Responder Analysis Results for UPDRS (Parts II+III) in Subjects who Completed 6, 12, and 18 Months of Rotigotine Maintenance (Pool E2)

Previous Treatment Group in Double-Blind Part of Trial	Duration of Rotigotine Maintenance					
	6 Months		12 Months		18 Months	
	n[a]	20% responders (%)	n[a]	20% responders (%)	n[a]	20% responders (%)
Overall	468	55	273	48	99	42
Placebo	104	49	31	45	0	-
Rotigotine	274	56	239	49	99	42
Ropinirole	90	59	3	67	0	-

UPDRS = Unified Parkinson's disease rating scale

a The number of subjects is the number who received rotigotine, who had a UPDRS score within 42 days of the endpoint, and whose data were available as of the data cut-off of this submission. Because of the less frequent trial visits in the open-label extension trials (ie, every 3 months compared with every month in the double-blind trials) some subjects did not have a UPDRS score within the analysis windows. Thus, the number of subjects with UPDRS data (n) is lower than the number of subjects actually participating in the trials.

Change from Baseline in the UPDRS Subtotal (Parts II+III) in Subjects who Completed 6, 12, and 18 Months of Rotigotine Maintenance (Pool E2)

Previous Treatment Group in Double-Blind Part of Trial	Duration of Rotigotine Maintenance					
	6 Months		12 Months		18 Months	
	n[a]	Change	n[a]	Change	n[a]	Change
Overall	468	-7.0	273	-6.2	99	-4.3
Placebo	104	-4.7	31	-1.7	0	-
Rotigotine	274	-6.9	239	-6.6	99	-4.3
Ropinirole	90	-9.8	3	-17.3	0	-

UPDRS = Unified Parkinson's disease rating scale

a The number of subjects is the number who received rotigotine, who had a UPDRS score within 42 days of the endpoint, and whose data were available as of the data cut-off of this submission. Because of the less frequent trial visits in the open-label extension trials (ie, every 3 months compared with every month in the double-blind trials) some subjects did not have a UPDRS score within the analysis windows. Thus, the number of subjects with UPDRS data (n) is lower than the number of subjects actually participating in the trials.

- Discussion on clinical efficacy

Pharmacokinetic data support the use of transdermal delivery for the administration of rotigotine. The main features derive from its metabolism (high conjugation pattern of unchanged drug and dealkyl metabolites). Dealkylation shows no specific isoforms dependence, therefore genetic differences, drug-drug interaction studies and renal/hepatic impairment studies could be limited. No clinical relevant effects following interaction with CYP iso-enzymes that are involved in rotigotine metabolism are expected. The inter-individual variability in rotigotine plasma levels was extensive. This should not be a major issue in clinical practice since rotigotine dosages will be titrated individually based on clinical response.

In patients with mild to severe renal dysfunction or with moderate hepatic impairment, only little accumulation of the biological active parent drug was found. Again, rotigotine will be titrated individually and therefore no serious clinical side effects are to be expected in patients with chronic renal or hepatic impairments. However, in acute onset of renal dysfunction unexpected increments of rotigotine levels might occur, and rotigotine dosage should be adjusted in such clinical conditions.

The demonstration of efficacy for rotigotine in early PD is essentially derived from a large dose dose-finding study – SP 506 and 2 pivotal studies (SP 512 and SP513 which included a comparison with ropinirole). In these studies, rotigotine consistently had a beneficial effect in the signs and symptoms of early PD. The dose-finding study showed the 13.5mg/d dose as the optimal dose with no extra gain for 18 mg/d seen in this study. These findings defined the dose range tested in the pivotal studies. However from the data obtained in these pivotal studies it is likely that 18 mg/d is more efficacious than 13.5 mg/d and it is possible that dose higher than 18 mg/d could be useful if tolerated.

The pivotal studies show that rotigotine is efficacious in the treatment of early PD patients. The effect size is about 5 points in UPDRS II+III, as compared to placebo at 6 months of treatment; out of those 5 points, about 4 are derived from part III. The rate of responders was always in favor of rotigotine; for the 20% improvement definition rotigotine responders were about 50% (in placebo groups it varies from 20 to 30% approximately) and for the 30% improvement definition rotigotine responders were about 40% (in placebo groups it varies from 15% to 25% approximately).

Nevertheless, the 3-arm pivotal trial rotigotine failed to prove non-inferiority to ropinirole. In fact ropinirole was substantially more efficacious that rotigotine which raised discussions on the benefit of rotigotine. Since almost all rotigotine patients reached the maximal study dose of 18mg/d, the optimal dose could be higher if well tolerated, but such data were not available. This also might explain the

observation that for rotigotine the long-term efficacy appears to wear off which was not the case for ropinirole.

Trial characteristics cannot explain the difference since study SP513 was a randomised double-blind placebo and positive controlled parallel group trial where baseline characteristics are equally distributed over the study arms.

Rotigotine effect size was in line with what is expected for a dopamine agonist. Ropinirole responder rate in study SP513 (70% for the 20% responder definition) was greater than usually seen in ropinirole studies but the highest mean dose of ropinirole in those literature trials is 16 mg/d and the lowest 8.3mg/d while in study SP513 one third of the ropinirole subjects reached 24 mg/d.

If some benefits of the transdermal device were acknowledged (i.e. once daily doses, easy titration, and circumvention of oral administration with no relevant drug or food interactions), other were considered only potential without confirmative data (i.e. continuous drug delivery with more constant levels of a dopamine-agonist potentially reducing risks of early-morning motor impairment, occurrence of dyskinesias, somnolence or hallucinations).

In fact, the lower efficacy of rotigotine as compared to ropinirole would only be a concern if the use of rotigotine would prevent patients to have a better treatment but this is not the case because patients are individually titrated to optimal control of symptoms. When a treatment is not satisfactory patients may be switched to alternative treatment, including other dopamine agonists.

Experience using higher dose is limited in open-label trials in patients with early Parkinson Disease. Higher doses of rotigotine up to 36.0mg/day are currently under investigation for treating the signs and symptoms of advanced-stage Parkinson's disease.

The applicant proposes to commercialize a "treatment initiation pack " containing 28 transdermal patches in 4 cartons containing 7 patches of 2mg/24h, 7 patches of 4mg/24h, 7 patches of 6mg/24h, and 7 patches of 8mg/24h. This starter pack can be a useful tool to ensure a smooth titration to the individual optimal dose. The package and the package leaflet should allow easy understanding of the titration scheme and correct administration during the titration phase at the initiation of therapy. It is therefore acceptable.

Clinical safety

At the beginning of the rotigotine development program, silicone- and acrylic-based prototype formulations were used. Further development by Schwarz was performed with silicone-based patches that had a decreased drug load and higher relative bioavailability compared to the acrylic-based formula. The initial silicone patch manufacturing process started with rotigotine hydrochloride. Patches manufactured according to this procedure were used in early Phase 1 and Phase 2 clinical trials. The manufacturing process was changed later using rotigotine base as the starting material. These patches, manufactured according to the final process, were used in most of the clinical pharmacological trials as well as in the pivotal Phase 3 trials.

All subjects receiving at least 1 dose of trial medication (silicone patch formulation, ropinirole, or placebo) by 31 Dec 2003 were included in the pooled safety analyses.

For safety several safety analysis pools were defined (S1-S11). The most important once are described here and tabulated in section patient exposure:

- Safety pool S1 included the double-blind phase of the primary clinical trials, i.e. studies SP506, SP512 and SP513 in early Parkinson's Disease.
- Safety pool S2 included all double-blind phase 2/3 subjects with early-stage Parkinson's disease, i.e. SP534, SP540, SP535, SP506, SP512 I (DB) and SP513 Part I (DB).
- Safety pool S3 included all phase 2/3 subjects with early-stage Parkinson's disease including the open-label data. In this pool, subjects originally on placebo or ropinirole receiving rotigotine in the open label extension were incorporated in the rotigotine arms.
- Safety pool S4 included the subjects of the pivotal studies only i.e. SP512 Part I (DB) and SP513 Part I (DB).

- Safety pool S5 included phase 3 subjects with early-stage Parkinson's disease treated at least once in open-label. For the subjects receiving placebo or ropinirole in the double-blind, only the open-label data for exposure to rotigotine were displayed.
- Safety pool S6 included all phase 3 subjects with early-stage Parkinson's disease treated at least once. Only the open label data were used.

Safety pool S1 is referred to as "Primary safety pool" and safety pools S5 and S6 is referred to as "Data from long-term trials."

The safety pools excluded phase 1 and 2a trials. Safety of these trials were reported on a by trial basis. The other safety pools incorporated patients/healthy volunteers other than early Parkinson's Disease.

- Patient exposure

The overall rotigotine exposure with the final silicone formulation is summarised in the table below.

Overall rotigotine exposure with final silicone formulation

Population	Subjects n (%)	Subject-years of exposure
Phase 1		
Healthy volunteers	547	—
Subjects with hepatic or renal impairment	33	—
Subjects with early-stage Parkinson's disease	70	—
Phase 2/3		
Subjects with early-stage Parkinson's disease		
>0 months	1017 (100)	716
>6 months	535 (53)	612
>12 months	302 (30)	437
>24 months	3 (<1)	6.1
Subjects with advanced-stage Parkinson's disease		
>0 months	268 (100)	58
Subjects with restless legs syndrome[a]		
>0 months	73 (100)	1.7

a This population includes 24 subjects who participated in a Phase 1 trial (SP628).

NOTE: Table does not include subjects in trials where trial medication remained blinded as of 31 Dec 2003.

A total of 1301 subjects with early-stage Parkinson's disease received trial medication in 8 clinical trials, of which a total of 1087 subjects received rotigotine (70 in one Phase 1 trial, 312 in 5 Phase 2 trials and 705 received rotigotine in two Phase 3 trials [SP512 and SP513] each of which included a 6-month double-blind portion and a long-term [=12 months] open-label portion).

164 subjects received a modal dose of 13.5mg/day for at least 1 year and 122 subjects a modal dose of ≥18.0mg/day for at least 1 year.

- Adverse events

In the main studies (Pool S1), 74% of the patients on placebo, 83% of the patients on rotigotine and 76% of the patients on ropinirole reported adverse events. The most common (≥5%) treatment-emergent AEs that occurred more frequently among rotigotine-treated subjects compared with placebo-treated subjects in Pool S1 included (in descending frequency) nausea, application site reaction, somnolence, dizziness, headache, vomiting, insomnia, fatigue, back pain, and constipation.

Treatment-emergent adverse events occurring in at least 5% of subjects in the rotigotine group during treatment – Pool S1

Body system/preferred term	Placebo N=289 n (%)	Rotigotine N=649 n (%)	Ropinirole N=228 n (%)
Any body system	213 (74)	538 (83)	173 (76)
Application site disorders			
Application site reaction	40 (14)	239 (37)	17 (8)
Body as a whole – general disorders			
Fatigue	20 (7)	49 (8)	14 (6)
Central & peripheral nervous system disorders			
Dizziness	32 (11)	118 (18)	39 (17)
Headache	30 (10)	88 (14)	20 (9)
Gastrointestinal system disorders			
Nausea	43 (15)	244 (38)	82 (36)
Vomiting	6 (2)	81 (13)	25 (11)
Constipation	11 (4)	35 (5)	20 (9)
Musculoskeletal system disorders			
Back pain	15 (5)	36 (6)	12 (5)
Psychiatric disorders			
Somnolence	45 (16)	161 (25)	67 (29)
Insomnia	14 (5)	64 (10)	14 (6)
Respiratory system disorders			
Upper respiratory tract infection	16 (6)	34 (5)	12 (5)

Data source: ISS Table 25.1

For Pool S1, 74% of placebo-treated subjects, 83% of rotigotine-treated subject, and 76% of ropinirole-treated subjects reported 1 or more AEs (ISS Table 25.1). The most common (≥5%) treatment-emergent AEs that occurred more frequently among rotigotine-treated subjects compared with placebo-treated subjects included (in descending frequency) nausea (38% rotigotine vs 15% placebo), application site reaction (37% vs 14%), somnolence (25% vs 16%), dizziness (18% vs 11%),

With the exception of application site reactions, the most common AEs occurred in a similar proportion of rotigotine- and ropinirole-treated subjects.

Adverse events that occurred at a rate of at least 1% in the rotigotine group and at least twice as often as in the placebo group were considered to be “drug associated”.

Common (at least 1%) drug-associated adverse events – Pool S1

Preferred term	Placebo N=289 n (%)	Rotigotine N=649 n (%)	Ropinirole N=228 n (%)
Application site reaction	40 (14)	239 (37)	17 (8)
Mouth dry	4 (1)	20 (3)	6 (3)
Fever	1 (<1)	9 (1)	1 (<1)
Gait abnormal	0	12 (2)	2 (1)
Confusion	1 (<1)	9 (1)	9 (4)
Nausea	43 (15)	244 (38)	82 (36)
Vomiting	6 (2)	81 (13)	25 (11)
Dyspepsia	4 (1)	24 (4)	13 (6)
Anorexia	3 (1)	18 (3)	4 (2)
Hiccup	0	11 (2)	2 (1)
Gastroesophageal reflux	0	8 (1)	1 (<1)
QT increased	1 (<1)	8 (1)	0
Insomnia	14 (5)	64 (10)	14 (6)
Hyperglycemia	2 (1)	9 (1)	3 (1)
Dreaming abnormal	1 (<1)	22 (3)	1 (<1)
Hallucination	2 (1)	13 (2)	13 (6)
Sleep attacks	0	9 (1)	4 (2)
Pharyngitis	0	11 (2)	7 (3)
Rash erythematous	2 (1)	15 (2)	2 (1)
Urinary tract infection	4 (1)	18 (3)	4 (2)
Urinary incontinence	2 (1)	9 (1)	1 (<1)
Pyuria	1 (<1)	7 (1)	0
Vision abnormal	2 (1)	19 (3)	2 (1)

Data source: ISS Table 42.1 M2, V8, 2.7.4

In Pool S1, over half of the subjects in each treatment experienced AEs considered by the investigator to be related to trial medication: 57% in placebo, 76% in rotigotine, and 70% in ropinirole. The most common (≥5%) of these were all widely recognized class effects of dopamine agonists, or associated with transdermal delivery systems.

The high incidence rates of nausea, somnolence, dizziness, headache, vomiting observed in the titration phase dropped drastically in the maintenance period. The incidence rates of nausea and vomiting remained relatively high (about 5%) as compared to placebo, whereas the incidences of somnolence, dizziness, headache and insomnia (range 3.6%-8.1%) were comparable to those of placebo.

There was no evidence of a withdrawal effect for rotigotine or ropinirole.

- Serious adverse event/deaths/other significant events

Three subjects with early-stage Parksinson's disease died during the clinical development program for rotigotine as of the clinical cutoff date (3/1231; 0.2%). One early-stage Parkinson's subject who died received rotigotine (1/1017, 0.1%), while 2 subjects who died received ropinirole (2/228, 0.9%). Four additional deaths were reported in trials on subjects with advanced-stage Parkinson's disease

In Pool S1, 6% (17/289) of placebo-treated subjects reported 23 SAEs, 7% (44/649) of rotigotine-treated subjects reported 58 SAEs, and 14% (31/228) of ropinirole treated subjects reported 39 SAEs. In all treatment groups, SAEs occurred across multiple body systems with no obvious trends. Except application site reaction; all other AEs considered related to trial medication per investigator occurred in less than 3 subjects.

Application site reactions commonly occur with the rotigotine patch but are usually localized and mild or moderate in intensity. The reactions were similar in short-term and long-term trials in subjects with early Parkinson's disease. Most subjects with these reactions continued treatment. The reactions usually subsided after variable time periods or removal of the patch. In three cases the application side

reaction were reported as serious. The severe reactions concerned contact dermatitis, allergic dermal reaction at site of application and itching.

Local tolerance (cumulative irritation) and sensitization of the transdermal system (rotigotine 1.125 mg /2.5 cm^2) has been studied in healthy subjects (studies SP629 and SP673 respectively). Study 629 was a randomised, blind, placebo-controlled local tolerance study in 38 healthy volunteers. Study 673 was a randomised, blind, placebo controlled skin sensitisation study in 229 healthy subjects. Local tolerance was assessed by the dermal response score (0= no evidence of irritation, 7 = strong reactions spreading beyond test site) after repetititve application of rotigotine or placebo patch compared to daily rotational application of the rotigotine patch. This trial also included the repetitive application of a negative and a positive control. Repetitive application was stopped after induction of a predefined maximum irritation score of 3 (= erythema and papules; SP629) or 2 (=definite erythema, readily visible; or minimal edema or minimal papular response; SP673). The irritation score observed in SP673 was low (0.29) and was similar to that obtained after daily rotating patch application in SP629 (0.34). In study SP673, a sensitization trial including 229 subjects, no case of sensitization to rotigotine and placebo patches was observed. In contrast, in study SP629 a classical type IV contact dermatitis according to Coombs and Gell was confirmed by skin biopsies after rechallenge in 2 subjects, whereas in 1 subject it could not be differentiated from toxic dermatitis. This was explained by the design of SP629 (more frequent repetitive patch application on the same skin site, mechanical stress by patch removal on the same skin site every 24 hours, positive controls in addition to rotigotine and placebo patches, continuing rotating application after induction of maximum irritation by repetitive application) which is very unlikely in a therapeutic setting. Overall, healthy volunteers testing showed that rotigotine is a mildly irritating substance and that reactions are reduced with patch rotation.

Other issues deserved special analysis since the drug being evaluated is a dopamine agonist.

Somnolence and sleep attacks:
Somnolence was reported at comparable rates in Pool S1 subjects receiving rotigotine (25%, 161/649) and ropinirole (29%, 67/228). Somnolence was reported in 16% (45/289) of subjects receiving placebo. Although somnolence was somewhat less common during the later months of maintenance than during titration and early maintenance, the percentage of rotigotine-treated subjects reporting somnolence was more consistent over time than for nausea and vomiting.
The SPC recommend that Prescribers continually reassess drowsiness or sleepness.

Orthostatic hypotension / Syncope
Suspected orthostatic hypotension was reported in 4.2%, 4.5% and 4.8% of the subjects in under placebo, rotigotine, and ropinirole respectively (S1 pool). Suspected orthostatic hypotension did not vary over time or dose, was not reported as a serious adverse event, and very few subjects discontinued or had dose reduction because of postural hypotension.
Syncope was reported in 0.7%, 1.1% and 3.7% of the subjects in under placebo, rotigotine, and ropinirole respectively (S1 pool). All cases of syncope in rotigotine-treated subjects were reported during titration or first 3 months in maintenance; within this timeframe, incidence of syncope did not vary substantially over time or with dose. Syncope was reported as a serious adverse event in 1% (2/228) of subjects treated with ropinirole and <1% (1/649) of subjects treated with rotigotine. Syncope led to discontinuation of 1 subject treated with placebo and 1 subject treated with rotigotine (<1% for both) and 2 subjects treated with ropinirole (1%).
The SPC recommends monitoring of blood pressure, especially at the beginning of treatment.

Peripheral oedema
Extremity oedema was reported in 5.5%, 6.6% and 4.4% of the subjects receiving placebo, rotigotine and ropinirole respectively (S1 pool). Extremity oedema was not reported as a serious adverse event. Two rotigotine-treated subjects discontinued trial medication as a result of peripheral oedema and 1 subject receiving ropinirole had a dose reduction as a result of dependent oedema.

Dyskinesia

Dyskinesia (dyskinesia in a strict sense + hyperkinesia + involuntary muscle contractions) were reported in 1.7%, 2.9% and 0.9% % of the subjects receiving placebo, rotigotine and ropinirole respectively (S1 pool). Dyskinesia did not lead to discontinuations or dose reductions.

Compulsive disorders including pathologic gambling, hypersexuality, increased libido, repetitive meaningless actions (punding) have been reported in patients treated with Neupro.

- Laboratory findings

The incidence of abnormal laboratory values reported was low. No abnormalities specific for rotigotine were observed except a decrease in prolactin levels which is a known class-effect of dopamine-agonists.

QT- prolonging potential of rotigotine:
Concern resulted in an extensive evaluation programme. For SP512 and SP513, standard 12-lead ECGs were repeatedly taken from pre-treatment until safety follow-up assessment.
In Pool S1 "QT increased" was reported as an adverse event in 1.2% of the rotigotine-treated subjects (8 events in 8/649 subjects) versus 0.3% of the placebo treated subjects (1/289 subjects) and none of the ropinirole-treated subjects. In Pool S3, 11 rotigotine-treated subjects (1.1%) were reported to have a QT prolongation.
Reviewing the QT data of the cases in which an adverse event of prolonged QT was reported, in none of the 1017 rotigotine-treated subjects was a QTc prolongation identified during treatment in comparison to baseline which may have a possible relationship between rotigotine and the event. For all events, more likely alternative etiologies were found or the QT prolongation was not confirmed by other available data.

- Safety in special populations

The adverse event profile of rotigotine was generally similar between the age-groups analyzed, and between males and females.

Nausea was less common among rotigotine-treated subjects ≥65 (30%) years of age than among those <65 (43%) years of age. Nausea was also less common among rotigotine-treated subjects ≥75 (26%) years of age than among those <75 (39%) years of age.

The numbers of subjects with hepatic impairment or renal impairment are too small to evaluate whether adverse event profile would differ with subjects with/without hepatic/renal impairment.

- Safety related to drug-drug interactions and other interactions

In vitro studies and clinical trials have concluded that rotigotine has a very low potential for drug-drug interactions.

- Discontinuation due to adverse events

Adverse events leading to discontinuation occurred in 6%, 13% and 13% in the placebo, rotigotine and ropinirole group respectively. These were dose related. Most frequent events leading to discontinuation are summarised in the table below.

Treatment-emergent adverse events leading to discontinuation of trial medication in at least 1% of subjects treated with rotigotine – Pool S1

Preferred term	Placebo N=289 n (%)	Rotigotine N=649 n (%)	Ropinirole N=228 n (%)
Any body system	18 (6)	86 (13)	30 (13)
Application site reaction	0	34 (5)	0
Nausea	0	13 (2)	6 (3)
Vomiting	0	8 (1)	2 (1)

Data source: ISS Table 53.1

An event that determined need for dose reduction was excessive sweating. Increased sweating is described as a phenomenon possibly related to the underlying disease and to dopaminergic treatment. In Pool S1, the incidence of "sweating increased" was comparable for rotigotine, placebo and ropinirole: 3.5% (23/649) of the rotigotine-treated subjects reported sweating under the terms listed above in comparison to 2.4% (7/289) of the placebo-treated subjects and 3.1% (7/228) of the ropinirole-treated subjects. Sweating was mainly observed during the titration period of rotigotine. In general, these events were mild or moderate in intensity and the rotigotine treatment was continued.

- Post marketing experience

Rotigotine was not been marketed in any region at the time of the assessment.

- Discussion on clinical safety

The safety profile of rotigotine was comprehensively described and it can be considered absolutely typical of a dopamine agonist. The dopaminergic adverse reactions like nausea, vomiting and somnolence dominate the picture. Safety of rotigotine was fully comparable to ropinirole safety. The only exception is the existence of skin reaction in the application site which was expected with a transdermal patch. Most of them were considered mild and they can be managed by the rotation of the patch site.

Other issue that deserves special analysis since the drug being evaluated is a dopamine agonist was somnolence and sleep attacks. Somnolence was relatively common 25% and sleep attacks although uncommon (1%) are present.

The pattern of deaths and serious AEs were in line with expectations for the disease and age strata. There was no peculiar finding in this set of data that could raise concern.

The ECG data was collected in a systematic way because of the concern of a potential QT prolongation based in *in vitro* studies with HERG channels. The clinical data, which was comprehensively acquired and analysed, do not suggest a drug associated potential to induce QT prolongation.

Potential drug induced valvulopathy should be matter of a pharmacovigilance plan. Pergolide has been associated with valvular heart disease. Other dopamine agonists might also be associated. It is not yet clear if this harmful effect is related only with ergot drugs, which rotigotine is not, or with other characteristics of certain dopamine agonists not yet defined. Being an agonist of the 5-HT2B receptors could be such characteristics but the involvement of this mechanism in not certain. Given the uncertainty surrounding the problem of dopamine agonists induced valvulopathy and the need to evaluate this risk pro-actively, the applicant agreed to further assess this potential risk as part of its updated pharmacovigilance plan.

The impact of hepatic and renal impairment in rotigotine PK was studied in dedicated trials albeit one can consider them limited because only the lower dose was tested. Nevertheless it is acknowledged the administration of higher doses of dopamine agonists to non-PD patients is limited by the side-effects. Thus, the conclusions that hepatic and renal impairment do not have impact on rotigotine PK and therefore no dose adjustment is needed are endorsed.

Rotigotine decreases prolactin secretion in humans.

1.5 Pharmacovigilance

Description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures.

The company commited to have the additional Standard Operating Procedures in place before the product is placed on the market which cover the following activities:

- electronic reporting,
- meeting CXMP commitments,
- maintenance and up-date of Pharmacovigilance planning,
- activities of the Qualified person.

Risk Management Plan

The applicant submitted a risk management plan.

The safety specifications were identified as follows:

Important identified risks:

- Application site skin reactions,
- Sleep attacks and somnolence,
- Postural/orthostatic hypotension.

Important potential risks (which cannot be excluded):

- Cardiovascular fibrosis (based on data on other dopamine agonists),
- Effect on retina (based on non-clinical data),
- Neuroleptic malignant syndrone after abrupt withdrawal (class effect).

Important missing information:
Neupro has not been investigated in patients with severe hepatic impairment.

Appropriate information have been included in the SPC to prevent risk, in particular recommendation for:

- Rotation of application site, avoidance of direct exposure to sunlight in case of skin reaction,
- Ophtalmologic monitoring,
- Assessment of patients for drowsiness or sleepness,
- Caution in patients with severe hepatic impairment,
- Recommendation of blood monitoring pressure, especially at the beginning of treatment,
- Recommendation for not using rotigotine during pregnancy and discontinuing breast-feeding
- In case of treatment discontinuation, the daily dose should be reduced gradually,
- Caution when treating patients with severe hepatic impairment.

The Company will perform a post-approval safety study, where particular attention will be paid to any cardiac valve fibrosis related signs or symptoms. In addition, rotigotine will be included in an independent prospective study on cardiac fibrosis in Parkinson's disease patients on dopamine agonists.

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.

1.6 Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

Rotigotine belongs to the group of non-ergolinic dopamine agonists. Rotigotine resembles dopamine in respect to structure, receptor binding and functional activity.

Rotigotine affected action potential duration and hERG-mediated potassium current at concentrations that far exceed (143 and 214 times, respectively) human unbound mean peak plasma concentrations achieved at 18 mg.

In repeated dose and long-term toxicity studies, the major effects were associated with the dopamine agonist related pharmacodynamic effects and the consequent decrease of prolactin secretion.
Retinal degeneration was observed in albino rats. The effects were more pronounced in female rats. The relevance of these findings to humans is not known but ophtalmologiccal monitoring is recommended.

In a carcinogenicity study, male rats developed Leydig cell tumours and hyperplasia. These changes are well-known effects of dopamine agonists in rats after life-long therapy and assessed as not relevant to man.

Rotigotine did not induce gene mutations in the Ames test, but did show effects in the in vitro Mouse Lymphoma Assay with metabolic activation and weaker effects without metabolic activation. This mutagenic effect could be attributed to a clastogenic effect of rotigotine. This effect was not confirmed in vivo in the Mouse Micronucleus Test in the rat Unscheduled DNA Synthesis (UDS) test. Since it ran more or less parallel with a decreased relative total growth of the cells, it may be related to a cytotoxic effect of the compound. Therefore, the relevance of the one positive in vitro mutagenicity test is not known.

Rotigotine did not influence male fertility in rats, but clearly reduced female fertility in rats and mice, because of the effects on prolactin levels which are particularly significant in rodents. Rotigotine was embryotoxic in rats and mice at materno-toxic doses. Rotigotine should not be used during pregnancy. Inhibition of lactation is expected and rotigotine was excreted in breast milk in rats. Breast-feeding should be discontinued.

Based on local tolerance studies, effects due to the application and removal procedure of patches were identified after repeated patch administration to the same sites. Therefore, a rotating application scheme of rotigotine patches in human use is strongly recommended.

The environmental risk assessment could not be completed. The Applicant was asked to further assess the environmental risk and has committed to perform further studies on Environmental Risk Assessment (ERA).

Any used or unused patches should be disposed of in accordance with local requirements or returned to the pharmacy. Patches should not be flushed down the toilet nor placed in liquid waste disposal system.

Efficacy

The transdermal patch demonstrated to be a feasible formulation. The inter-individual variability in rotigotine plasma levels was extensive. This might form no severe obstacle in clinical practice, since rotigotine dosages will be titrated individually based on clinical response. No clinical relevant effects following interaction with CYP iso-enzymes that are involved in rotigotine metabolism are expected.

The efficacy for rotigotine in early PD as monotherapy is essentially derived from a large dose dose-finding study – SP 506 and 2 pivotal studies (SP 512 and SP513). Studies show consistently that rotigotine do have a beneficial effect in the signs and symptoms of early PD. The dose-finding study pointed to the 13.5 mg/d dose as the optimal dose, however, from the data obtained in the pivotal studies it is likely that 18 mg/d is more efficacious than 13.5 mg/d.

The pivotal studies clearly show that rotigotine is efficacious in the treatment of early PD patients. The effect size is about 5 p in UPDRS II+III, as compared to placebo at 6 months of treatment; out of those 5p, about 4p are derived from part III. The rate of responders was always in favor of rotigotine with a mean excess of responders of about 20 to 30%, compared to placebo.

However, in the 3-arm pivotal trial (SP513) rotigotine failed to prove non-inferiority to ropinirole. In fact, the difference in effect between ropinirole and rotigotine was significant in favour of Ropinirole. In addition, it cannot be excluded that efficacy may wear-off at long-term.

Safety

The safety profile of rotigotine can be considered typical of a dopamine agonist, with in particular dopaminergic AE like nausea, vomiting and somnolence. The only exception is the existence of skin reaction in the application site which is expectable in a transdermal patch. The large majority of these are considered mild and they can be managed by the rotation of the patch site.

The evaluation of the potential for QT prolongation does not suggest such a potential.

Theoritical risk for drug induced valvulopathy will be further assessed in the framework of a risk management plan.

Safety specifications have been defined and appropriate information to prevent risks have been included in the product information. No additional risk minimisation activities are required beyond those included in the product information.

The applicant performed a user consultation testing of the package leaflet including the treatment initiation pack.

Benefit-Risk assessment

Overall, even though ropinirole was substantially more efficacious in one study, rotigotine has shown a consistent and clinically relevant effect with an acceptable safety profile. Therefore, the benefit risk ratio is considered favorable in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease provided that a balanced description of the 3-arm trial is included in section 5.1 of the SPC. If a patient is insufficiently controlled while on treatment with rotigotine switching to another dopamine agonist might provide additional benefit.

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

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns,
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Neupro in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was favourable and therefore recommended the granting of the marketing authorisation.