SP0976, 2010-021394-37

CLINICAL STUDY REPORT SYNOPSIS

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This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB Pharma S.A.

Allée de la Recherche 60

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Official study title:

Multicenter, double-blind, placebo-controlled, parallel-group, Phase IV study to assess the effect of rotigotine on non-motor symptoms in patients with idiopathic Parkinson's disease

CLINICAL STUDY REPORT SYNOPSIS: SP0976

Name of company: UCB Pharma	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Neupro®	**Volume**: Not applicable	
Name of active ingredient: Rotigotine	**Page:** Not applicable	

Title of study: Multicenter, double-blind, placebo-controlled, parallel-group, Phase IV study to assess the effect of rotigotine on non-motor symptoms in patients with idiopathic Parkinson's disease

Investigator(s): Seventy-two investigators enrolled subjects in this multicenter study.

Study site(s): This was a multicenter study conducted in 12 [redacted] countries [redacted]). Overall, 72 sites participated in this study.

Publication(s) (reference[s]): No publications on this study are available at the time of the report.

Study period: The total study duration per subject was up to approximately 29 weeks. **First subject enrolled:** 23 Feb 2011 **Last subject completed:** 20 Nov 2012	**Phase of development:** Phase 4

Objective(s): The primary objective of this study was to demonstrate that rotigotine improves nonmotor symptoms compared to placebo in subjects with Parkinson's disease.

The secondary objective was to demonstrate that rotigotine is effective on motor symptoms and improves health-related quality of life (HRQL) compared to placebo in subjects with Parkinson's disease.

Methodology: SP0976 was a Phase 4, parallel-group, double-blind, randomized, placebo-controlled, multicenter study to evaluate the effect of rotigotine on nonmotor symptoms and to demonstrate that rotigotine is effective on motor symptoms and improves HRQL compared to placebo in subjects with idiopathic Parkinson's disease. Subjects successfully completing the Screening Period (Day -28 to Day -1) proceeded to Baseline (Day 1), were randomized, and started the Titration Period with a daily administration of rotigotine 2mg/24h for 1 week for subjects with early-stage Parkinson's disease (subjects without concomitant levodopa [L-DOPA] treatment) or with a daily administration of rotigotine 4mg/24h for subjects with advanced-stage Parkinson's disease (subjects with concomitant L-DOPA treatment). Doses were increased in weekly increments of 2mg/24h until the optimal dose (up to a maximum of rotigotine 8mg/24h for subjects with early-stage Parkinson's disease, or 16mg/24h for subjects with advanced-stage Parkinson's disease) was reached.

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Subjects randomized to placebo received matching placebo patches to maintain the blinding. The Titration Period lasted up to 4 weeks for subjects with early-stage Parkinson's disease and up to 7 weeks for subjects with advanced-stage Parkinson's disease. The 12-week Maintenance Period started once the subject had reached the maximum or optimal dose of rotigotine or matching placebo, and subjects remained on a stable dose of study medication throughout the Maintenance Period.

A De-Escalation Period followed completion of the Maintenance Period to allow for a gradual withdrawal from the study medication. Subjects' doses were reduced in 2mg/24h steps every other day to 2mg/24h for subjects with early-stage Parkinson's disease or to 4mg/24h, for subjects with advanced-stage Parkinson's disease, then to 0mg after 2 days. Dosing was completed on the day of removal of the final patch. The subjects returned for a Safety Follow-Up Visit 4 weeks after the final removal of the study medication.

Number of subjects (planned and analyzed): The sample size calculation was based on the primary efficacy variable. Using sample sizes of 222 subjects for rotigotine and 111 subjects for placebo, and an assumed standard deviation of approximately 27.33 (as observed in SP889) for the change in the total Nonmotor Symptoms Scale (NMSS) score, the power of 80% was expected to detect any differences between placebo and rotigotine. An effect of 8.94 points was anticipated.

Diagnosis and main criteria for inclusion: Subjects enrolled were ≥18 years of age, male or female, with diagnosed idiopathic Parkinson's disease with at least 2 of the following cardinal signs being present: bradykinesia, resting tremor, rigidity, or postural instability, and without any other known or suspected cause of Parkinsonism.

The main inclusion criteria for subjects included the following:

- Subject had a Hoehn and Yahr stage score ≤4.
- Subject had a total NMSS score ≥40.
- If the subject was receiving anticholinergics, monoamine oxidase (MAO) B inhibitors, or amantadine, he/she was to be on a stable dose for at least 28 days prior to the Baseline Visit and had to be maintained on that dose for the duration of the study.

If the subject was taking L-DOPA, he/she was to be on a stable dose of L-DOPA (in combination with benserazide or carbidopa) for at least 28 days prior to the Baseline Visit.

Test product, dose(s) and mode of administration, batch number(s): The investigational medicinal product (rotigotine) was supplied in an adhesive matrix on a silicone-based transdermal patch.

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The transdermal patch was administered once daily.

Doses were as follows: 2mg/24h, 4mg/24h, 6mg/24h, 8mg/24h, 10mg/24h, 12mg/24h, 14mg/24h, and 16mg/24h. Doses above 8mg/24h were delivered as a combination of suitable patch sizes.

Study medication was dispensed from the following batches:

10cm^2: [redacted]
20cm^2: [redacted]
30cm^2: [redacted]
40cm^2: [redacted]

Duration of treatment: The expected maximum duration of the treatment per subject was up to approximately 25 weeks, depending on the optimal treatment dose.

For subjects with early-stage Parkinson's disease, the maximum Titration Period was 4 weeks and for subjects with advanced-stage Parkinson's disease, the maximum Titration Period was 7 weeks. A 12-week Maintenance Period started once a subject attained the optimal or maximum dose. The De-Escalation Period lasted up to 12 days.

Reference therapy, dose(s) and mode of administration, batch number(s): Matching placebo patches were administered transdermally once daily with a silicone-based patch. The placebo patches as reference therapy corresponding to the following doses of investigational medicinal product (IMP) were available: 2mg/24h, 4mg/24h, 6mg/24h, 8mg/24h, 10mg/24h, 12mg/24h, 14mg/24h, and 16mg/24h. Doses above 8mg/24h were delivered as a combination of suitable patch sizes. Study medication (placebo patches) was dispensed from the following batches:

10cm^2: [redacted]
20cm^2: [redacted]
30cm^2: [redacted]
40cm^2: [redacted]
Training kits: [redacted]

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Criteria for evaluation:

Efficacy: The primary efficacy variable was the change from Baseline to the end of the Maintenance Period in the 30-item NMSS total score.

The secondary efficacy variables included the change from Baseline to the end of the Maintenance Period in the total Unified Parkinson's Disease Rating Scale (UPDRS) Part III score, in the HRQL measured by the 39-item Parkinson's disease questionnaire (PDQ-39), and in each of the 9 subdomains of the NMSS score (cardiovascular including falls, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, or miscellaneous).

The other efficacy variables included the Clinical Global Impression (CGI) and the Patient Global Impression (PGI) subscales of global improvement.

Safety: Safety was evaluated by the occurrence of adverse events (AEs), urine pregnancy tests in female subjects of childbearing potential, vital sign parameters (pulse rate, blood pressure), and by modified Minnesota Impulsive Disorders Interview (mMIDI).

Statistical methods: The primary variable was the change from Baseline to the end of the Maintenance Period in total NMSS score. All 30 NMSS items had to be available to calculate the NMSS total score. Each item was scored for frequency and for severity. Testing was performed using an analysis of covariance (ANCOVA) model, including factors for the treatment assignment (main factor), geographic region of the subject's investigational center, Parkinson's disease stage, early Parkinson's disease (subjects without concomitant L-DOPA treatment) or advanced Parkinson's disease (subjects with concomitant L-DOPA treatment) (stratifying factors as defined in the clinical database), and the Baseline Visit value of the total NMSS score as a covariate. The primary analysis of the primary variable was based on the Full Analysis Set (FAS). A sensitivity analysis was performed on the primary analysis model based on the FAS population, with the Parkinson's disease stage factor as reported in the Interactive Voice Response System (IVRS).

A secondary analysis of the primary efficacy variable was performed on a subset of the overall study population.

No multiplicity adjustments were performed as secondary objectives are supportive to the primary objective. All secondary efficacy objectives were analyzed as the change from Baseline to the end of the Maintenance Period for the FAS. The secondary efficacy variables analyzed as the change from Baseline to the end of Maintenance included the following: total UPDRS Part III score, PDQ-39, and each of the 9 NMSS subdomains (cardiovascular including falls,

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sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function, and miscellaneous). The change was analyzed using an ANCOVA model, including factors for the treatment assignment (main factor), country, Parkinson's disease stage (early or advanced, and stratifying factors), and the Baseline Visit value of the secondary objective score as a covariate.

All other statistical analyses were exploratory and summarized descriptively.

Absolute and relative frequencies of subjects were calculated for categorical variables. Summary statistics, such as mean, standard deviation, median, minimum, and maximum were presented for continuous variables.

Adverse events and diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 9.1. Medication was coded using the World Health Organization-Drug Registration and Listing (WHO-DRL) dictionary (Version Q2/2004).

Summary and conclusions:

Subject disposition: Overall, 377 subjects signed the informed consent, 28 subjects were screen failures, and 349 subjects were randomized to a treatment group. Three hundred forty-eight subjects received at least 1 dose of investigational medicinal product (IMP) and were included in the Safety Set (SS). A total of 333 subjects were included in the FAS. Of all subjects, 284 subjects constituted the Completers Set (CS) and completed the Maintenance Period.

The most common reason for discontinuation in both treatment groups were AEs (36 subjects [10.3%]) and withdrawal of consent (22 subjects [6.3%]).

Efficacy results: In this double-blind, placebo-controlled study, an improvement of nonmotor symptoms subjects with Parkinson's disease, assessed by the primary variable, NMSS total score, was observed in both the rotigotine and placebo groups.

Although improvement of the NMSS total score in rotigotine-treated subjects (-23.1 [SD: 23.4]) was greater than in placebo-treated subjects (-19.1 [SD: 24.2]), the treatment difference between rotigotine and placebo (-3.58 points, based on an ANCOVA) was not statistically significant (p=0.147; CI:-8.43 to -1.26). The clinical relevance of the difference in the change from Baseline in the NMSS total score was negligible.

For the analysis of the change in total NMSS score from Baseline to the end of the Maintenance Period by domain and subgroup, an improvement was generally observed in both treatment arms, with rotigotine-treated subjects showing a numerically greater change (indicating improvement) than placebo-treated subjects in sleep/fatigue, mood/cognition, and miscellaneous.

For the secondary variable on motor symptoms, measured by the UPDRS Part III score, the

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treatment difference between rotigotine and placebo based on an ANCOVA was -2.60 points (p=0.002; CI:-4.27 to -0.92). There was a greater improvement in rotigotine-treated subjects (-5.7 [SD: 8.0]; FAS) compared with placebo-treated subjects (-3.6 [SD: 8.3]; FAS).

The change in HRQL measured by PDQ-39 total score was greater in rotigotine-treated subjects compared to placebo-treated subjects. The treatment difference between rotigotine and placebo based on an ANCOVA was -2.79 points (p=0.024; CI: -5.21 to -0.37). There was a greater improvement in rotigotine-treated subjects (-6.1 [SD: 10.9]; FAS) compared with placebo-treated subjects (-2.7 [SD: 12.5]; FAS).

For the CGI, a higher percentage of rotigotine-treated subjects showed improvement (9% very much improved, 28.0% much improved, and 33.6% minimally improved) compared to the placebo-treated subjects (3.3% very much improved, 13.1% much improved, and 40.2% minimally improved).

For the PGI, a higher percentage of rotigotine-treated subjects showed improvement (5.2% very much improved, 31.8% much improved, and 35.1% minimally improved) compared to the placebo-treated subjects (4.9% very much improved, 16.4% much improved, and 36.1% minimally improved).

Overall, treatment differences in favor of rotigotine were observed for the PDQ-39 total score and the UPDRS Part III score. In addition, a higher percentage of rotigotine-treated subjects compared to placebo-treated subjects showed improvement in the CGI and PGI.

Safety results: Subjects with early and advanced Parkinson's disease were treated with their optimal dose or the maximum dose of rotigotine or placebo for a mean duration of 112 days (SD: 37.3) and 116 days (SD: 36.6), respectively.

Overall, rotigotine was well tolerated during the study. Most AEs were consistent with the stimulation of dopamine receptors, the use of a transdermal patch, and the clinical picture of the subjects' underlying disease. The majority of AEs were mild or moderate in intensity.

Two hundred eighty-four subjects (75.3%) randomized completed the Maintenance Period; 104 subjects received placebo and 180 received rotigotine. The most common reasons for discontinuation were withdrawal of consent and AEs, both similarly distributed across treatment groups. Discontinuation due to AEs was observed in 10.3% of the subjects in the study.

A total of 492 treatment-emergent adverse events (TEAEs) were reported by 200 subjects during the conduct of this study. Forty-eight percent of subjects in the placebo-treated group and 62.8% of the subjects in the rotigotine-treated group reported TEAEs.

For 4 placebo-treated subjects (3.2%) and 8 rotigotine-treated subjects (3.6%) in the SS serious adverse events (SAEs) were reported. For a total of 27 rotigotine-treated subjects and

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9 placebo-treated subjects AEs leading to discontinuation were reported. The most frequent AE leading to discontinuation for rotigotine-treated subjects was hypertension.

Overall, 3 subjects died. Two deaths were reported in the rotigotine group (1 subject with cardiac failure in the treatment period and 1 subject with traumatic brain injury in the post-treatment period). One death of unknown origin was reported in the placebo group.

There were no clinically relevant changes or trends in the mean changes from Baseline to the end of Maintenance Visit for blood pressure or pulse rate. Approximately 8% of the subjects in the rotigotine group and 5% of the subjects in the placebo group had 1 or more positive modules on the mMIDI. For 1 subject in the placebo group and 2 subjects in the rotigotine group, interviews confirmed the diagnosis of an impulse control disorder (ICD) at the end of the Maintenance Period but not at Baseline. These events were recorded as AEs. The most frequent finding was punding, reported by 6 subjects at the Maintenance/Withdrawal Visit.

The safety profile was consistent with the known safety profile of rotigotine.

Conclusions: In this double-blind, placebo-controlled study, an improvement of nonmotor symptoms in subjects with Parkinson's disease, assessed by the primary variable, NMSS total score, was observed in both the rotigotine and placebo groups.

The improvement of nonmotor symptoms was marked and clinically relevant in both treatment groups. While the improvement was greater in rotigotine-treated subjects than in placebo-treated subjects, rotigotine did not demonstrate a statistically significant improvement over placebo. Moreover, the clinical relevance of the difference in the change from Baseline in the NMSS total score is negligible.

For the analysis of the change in total NMSS score from Baseline to the end of the Maintenance Period by domain and subgroup, an improvement was generally observed in both treatment arms, with rotigotine-treated subjects showing a numerically greater change (indicating improvement) than placebo-treated subjects in the domains sleep/fatigue, mood/cognition, and miscellaneous.

Greater improvements in rotigotine-treated subjects than in placebo-treated subjects were observed for motor symptoms (measured by UPDRS Part III), HRQL (measured by PDQ-39 total score), CGI, and PGI.

Overall, rotigotine was well tolerated during the study, and the safety profile was consistent with the known safety profile of rotigotine.

Report date: 17 Jul 2013