SP0882, 2006-005438-19

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

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 Deutschland GmbH

(formerly SCHWARZ PHARMA Deutschland GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

An explorative, multicenter, open-label pilot trial with Neupro® (rotigotine transdermal patch) once daily treatment administered perioperatively in patients with idiopathic Parkinson's disease

Name of company: SCHWARZ PHARMA Deutschland GmbH (A member of the UCB Group)	**Individual trial table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of finished product: rotigotine transdermal patch (Neupro®)	**Volume:** Not applicable	
Name of active ingredient: rotigotine	**Page:** Not applicable	

Title of trial: An explorative, multicenter, open-label pilot trial with Neupro® (rotigotine transdermal patch) once daily treatment administered perioperatively in patients with idiopathic Parkinson's disease

Investigators: This was a multicenter trial

Trial site(s): 12 sites in [redacted]

Publication (reference): None

Studied period (years): <1 **First subject enrolled**: 28 Oct 2007 **Last subject completed**: 26 May 2008	**Phase of development: 4**

Objectives: This pilot trial was designed to provide exploratory information on the feasibility of perioperative rotigotine treatment in a limited number of subjects with Parkinson's disease (PD). In addition, pharmacokinetics (PK), efficacy, and safety information on the use of rotigotine as part of the perioperative management of PD was collected.

Methodology: SP882 was an open-label, nonrandomized, multicenter, pilot trial to provide exploratory information on the feasibility of perioperative rotigotine treatment in a limited number of subjects with PD, as well as PK, efficacy, and safety information on the use of rotigotine as part of the perioperative management of PD. Subjects who successfully completed the Screening period were considered eligible to receive treatment in this trial.

The trial consisted of the Screening Phase (up to 28 days), Baseline visit (Day 1), Treatment (operative day [Day 2]; most subjects were to be treated with rotigotine patches for 1 or 2 days, although application could have lasted up to 2 weeks after surgery if necessary [eg, unexpected extended ventilation period postoperatively]), End of Treatment (postoperative day; day after last patch removal), and Safety Follow-Up (2 weeks after discharge from the hospital).

The subject's normal preoperative evening PD medication (except levodopa-containing preparations and cabergoline) were replaced by 1 rotigotine patch of 2mg/24h (10cm^2), 4mg/24h (20cm^2), 6mg/24h (30cm^2), or 8mg/24h (40cm^2) or by combining 2 rotigotine patches for the doses 10mg/24h (50cm^2), 12mg/24h (60cm^2), 14mg/24h (70cm^2), or 16mg/24h (80cm^2) at approximately 7:00pm the evening before surgery (surgery per protocol [SPP]), providing continuous perioperative dopaminergic stimulation. Levodopa could have been taken until 12 midnight on the preoperative day. Cabergoline was to be stopped 24 hours prior to the switch. The determination of patch dosage strength was to be based on the recommendations described in the "Test product, dose and mode of administration, batch number" section below, but the final decision of rotigotine dose selection was left to the discretion of the neurologist.

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Methodology (continued): After surgery, the subject's previous PD medication was to be resumed in the evening of the operative day or rotigotine treatment could have been maintained for up to 2 days, including the preoperative day. If required by the subject and the investigator (eg, unexpected extended ventilation period), rotigotine could have been applied for up to a maximum of 2 weeks following surgery and after notification of the sponsor.

Number of subjects (planned and analyzed): Approximately 10 to 15 sites were planned, 12 were initiated and 6 of these 12 enrolled at least 1 subject. A total of 30 subjects were planned to be screened, with a target of up to 20 subjects to be included in the trial; 14 subjects were enrolled in the trial.

Diagnosis and main criteria for inclusion: Included in this trial were male or female subjects who were ≥18 years of age and ≤80 years of age and who had idiopathic PD (early- or advanced-stage), as defined by the cardinal sign bradykinesia, plus the presence of at least one of the following: resting tremor, rigidity, or postural instability and is without any other known or suspected cause of Parkinsonism. Subjects had American Society of Anesthesiologists (ASA) stage II through III disease as determined by the investigator; were currently taking medication for PD (eg, levodopa, [redacted], entacapone, [redacted]); and were scheduled for an operation requiring general anesthesia.

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Test product, dose and mode of administration, batch number: The determination of patch dosage strength (as described in the "Methodology" section above) was based on the following recommendations, but the final decision of rotigotine dose selection was left to the discretion of the neurologist.

Conversion	mg/day prior PD medication	Equivalent to mg/24h rotigotine patch
Ropinirole to rotigotine	1-1.5	1
Pramipexole (salt) to rotigotine	1	4
Cabergoline to rotigotine	1	3
Levodopa to rotigotine	100	3-4

Note: 100mg of levodopa is assessed as equivalent to 3mg of ropinirole, 1-1.5mg of pramipexole (salt), and 1mg of cabergoline.

The last dose of cabergoline was administered 24 hours before the patch-application. The last administration of pramipexole, ropinirole, entacapone, [redacted], and [redacted] was at noon of the preoperative day. Levodopa-containing preparations continued to be administered through the evening dose on the preoperative day and could have been taken until 12 midnight on the preoperative day.

Test product, dose and mode of administration, batch number (continued): After surgery, the subject's previous PD medication was able to be resumed in the evening of the operative day or rotigotine treatment could have been maintained for up to 2 days, including the preoperative day. If required by the subject and the investigator (eg, unexpected extended ventilation period), rotigotine could have been applied for up to a maximum of 2 weeks following surgery and after notification of the sponsor.

All rotigotine patches used in this trial came from the batch number [redacted]

Duration of treatment: The treatment duration in this trial was at maximum 8 weeks and consisted of the Screening Phase (up to 28 days), Baseline visit (Day 1), Treatment (operative day [Day 2]), End of Treatment (postoperative day; day after last patch removal; this period could be extended up to 2 weeks if the intensive care unit was involved), and Safety Follow-Up (2 weeks after discharge from the hospital).

Reference therapy, dose and mode of administration, batch number: None

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Criteria for evaluation:

Efficacy: Efficacy variables were the assessments of feasibility by the anesthesiologist, the neurologist, and the subject. The feasibility of applying rotigotine transdermal patch during the perioperative period was evaluated as follows:

- Feasibility assessment questionnaire by the anesthesiologist (performed at Visit 3 [operative day; Day 2])
- Feasibility assessment questionnaire by the neurologist (performed at the Safety Follow-Up visit [Visit 5; 2 weeks after discharge])
- Feasibility assessment questionnaire by the subject (performed at the Safety Follow-Up visit [Visit 5; 2 weeks after discharge])

Pharmacokinetics/apparent dose: A blood sample for determination of the plasma concentration of unconjugated rotigotine was obtained prior to removal of the first patch (Day 2). Additionally, used patches were collected only after Day 1 (even if the subject was treated for a longer period). These removed patches from Day 1 were collected for determination of the apparent dose on Day 2.

Safety: The following safety variables were measured: observation and assessment of adverse events (AEs), laboratory parameters, vital signs measurements (blood pressure, pulse), physical (including neurological) examination findings, and 12-lead electrocardiogram (ECG) findings.

Statistical methods: No formal statistical testing was performed on any of the data collected in this trial. For each analysis, the analysis set used was specified. Continuous variables (or categorical variables with a clear ranking order) were summarized using univariate descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables were summarized using frequencies and percentages (n, %). Unless otherwise specified, percentages were calculated with a denominator using the number of subjects qualifying for the table or figure within each column group.

Each subject's postdose values were compared with the respective Baseline/predose value. Therefore, a change from Baseline approach was part of the statistical analysis, either numerical or as a shift table in case of categorical data. In this approach, Baseline was always defined as the last available valid measurement predose.

For coding and consolidating AEs and medical history (past and/or concomitant diseases) into categories of System Organ Classes, High Level Terms (only for AEs), and Preferred Terms, MedDRA Version 9.1 (Medical Dictionary for Regulatory Activities) or higher was used. Concomitant and previous medication were coded using the World Health Organization–Drug Reference List (WHO-DRL, Version 2004 second quarter), and diseases according to MedDRA Version 9.1 or higher.

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Summary and conclusions:

Efficacy:

- In this trial, for the 11 subjects who completed the feasibility assessment questionnaire and/or had it completed by the anesthesiologist or neurologist, a rating of 1 (I agree completely) was the most common response (7 to 10 subjects [63.6% to 90.9%, respectively]) to all questions.
- Only 1 subject had a rating of 6 (I don't agree at all), as noted by the neurologist, for the question "Re-switch was easily feasible." There were no ratings of 6 assessed by the anesthesiologist or the subject.
- The mean feasibility assessment ratings ranged from 1.1 to 1.5 (range 1 to 4) for all questions as assessed by the anesthesiologist, from 1.2 to 1.5 (range 1 to 6) for all questions as assessed by the neurologist, and from 1.2 to 1.5 (range 1 to 4) for all questions as assessed by the subject.
- Ten of the 11 subjects (90.9%) who completed the feasibility assessment questionnaire said that, if they had to undergo surgery again, they would choose the Parkinson patch. None of the subjects chose a rating of 6 (I don't agree at all).

Pharmacokinetics/apparent dose results:

Rotigotine plasma concentrations are in the same range as seen in various clinical trials. The overall mean measured apparent doses in percent at the Operative Day are around 39%. PK and apparent dose data are consistent with results observed in previous trials.

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Safety results:

In this open-label trial, subjects were treated before surgery with rotigotine of either 2mg/24h (10cm^2), 4mg/24h (20cm^2), 6mg/24h (30cm^2), or 8mg/24h (40cm^2) or by combining 2 rotigotine patches for the doses 10mg/24h (50cm^2), 12mg/24h (60cm^2), 14mg/24h (70cm^2), or 16mg/24h (80cm^2) for a mean duration of exposure of 1.8 days (ranged from 1 day to 5 days).

Rotigotine was generally well tolerated during the trial. Most AEs were consistent with the surgical procedure, stimulation of dopamine receptors, and the use of a transdermal patch. The majority of AEs were mild or moderate in intensity. During the trial, the most common treatment-emergent AEs (TEAEs) were procedural pain, constipation, nausea, urinary tract infection, iron deficiency, sleep disorder, and pruritus. There were no discontinuations because of AEs in the trial. Four treatment-emergent serious AEs (SAEs) were reported for 4 subjects; the SAEs included a [redacted], [redacted] and occurred in 1 subject each. The event of ventricular asystole was considered possibly related to the endoprothesis of right hip since its replacement was the reason for the surgery and the following blood loss, highly probably related to the blood loss during surgery, probably related to the trial medication (the second patch was applied 7 hours before the event occurred), and unlikely related to the trial design/procedure.

There were no deaths or other significant AEs during the trial.

There were no trends observed in laboratory parameters that were of clinical relevance. There was no indication for rotigotine to cause any clinically relevant ECG abnormalities or changes in this trial. No clinically relevant changes in vital signs or physical and neurological examinations were noted.

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Conclusions:

In summary, the objectives of this trial were met based on the following conclusions:

- The feasibility of applying rotigotine transdermal patch during the perioperative period was shown, as evidenced by response to questions on feasibility assessment questionnaires completed by the anesthesiologist, neurologist, and subject.
- Rotigotine plasma concentrations increased with dose.
- Rotigotine was generally well tolerated in this open-label trial. In general, AEs were consistent with the surgical procedure, stimulation of dopamine receptors, and use of transdermal patch.
- The most frequently occurring TEAEs were procedural pain, constipation, nausea, urinary tract infection, iron deficiency, sleep disorder, and pruritus.
- Four treatment-emergent SAEs were reported for 4 subjects; the SAEs included a [redacted] and occurred in 1 subject each.
- There were no deaths, other significant AEs, or discontinuations because of AEs in the trial.
- There were no apparent trends in laboratory abnormalities, vital signs, ECGs, or physical or and neurological examination findings throughout the trial.

Date of the report: 07 Apr 2009