SP0915, 2006-006907-35

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 BIOSCIENCES GmbH

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

A multicenter, multinational, Phase 3b, open-label extension trial to evaluate the long-term effect of the 24-hour transdermal delivery of rotigotine on motor function, sleep quality, and nocturnal and non-motor symptoms in subjects with idiopathic Parkinson's disease

CLINICAL TRIAL REPORT SYNOPSIS: SP915

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: Rotigotine transdermal system *	**Volume:** Not applicable	
Name of active ingredient: Rotigotine	**Page:** Not applicable	

Title of study: A multicenter, multinational, Phase 3b, open-label extension trial to evaluate the long-term effect of the 24-hour transdermal delivery of rotigotine on motor function, sleep quality, and nocturnal and non-motor symptoms in subjects with idiopathic Parkinson's disease **

Investigator(s): This was a multicenter, multinational trial involving 22 investigators.

Study site(s): Twenty-two trial sites in [redacted]

Publication(s) (reference[s]): None

Studied period: The trial duration was approximately 1 year from the start of the Titration Period to the Safety Follow-Up Visit. **First subject enrolled:** 30 Jul 2007 **Last subject completed:** 05 May 2009	**Phase of development:** Phase 3b

Objective(s): The objective of this open-label extension trial was to assess the long-term effect of the 24-hour transdermal delivery of rotigotine on motor function, sleep quality, and nocturnal and nonmotor symptoms of Parkinson's disease. The long-term safety and tolerability of the rotigotine transdermal patch was also evaluated.

Methodology:

SP915 was a Phase 3b, multicenter, multinational, open-label, extension trial of SP889 (RECOVER) to evaluate the effect of the 24-hour transdermal delivery of rotigotine on motor function, sleep quality, and nocturnal and nonmotor symptoms of Parkinson's disease. The trial consisted of a Titration Period (up to 8 weeks), a 10-month Maintenance Period, and a De-Escalation Period (up to 14 days), which was followed by a Safety Follow-Up Visit 28 days after the End of Treatment Visit. During the course of SP915, the manufacturing process for rotigotine patches was changed, requesting refrigerated storage of the patches. As the trial medication expired in Apr 2009 and in order to avoid switching to the refrigerated product, it was decided to stop enrollment into SP915 in Apr 2008 to ensure sufficient trial medication for all subjects enrolled at that time to complete the trial according to the protocol. This resulted in a lower enrollment to SP915 than originally anticipated.

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** The study was registered on EudraCT with the additional abbreviated title: 'Long-term extension of RECOVER' (this note was added for clarification purposes afterwards)

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Number of subjects (planned and analyzed):

Eighty-four subjects who fulfilled the eligibility criteria were allowed to enroll in this trial. The participation of approximately 270 eligible subjects was originally anticipated.

Diagnosis and main criteria for inclusion:

Subjects had to fulfill the following inclusion criteria:

1. The subject was informed and given ample time and opportunity to think about her/his participation and had given her/his written informed consent.
2. The subject was willing and able to comply with all trial requirements.
3. The subject had completed trial SP889.
4. The subject, in the opinion of the investigator, was expected to benefit from long-term treatment of rotigotine.

Test product, dose(s) and mode of administration, batch number(s):

Rotigotine was administered transdermally once daily with a silicone-based patch for a period of 24 hours. 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. Trial medication was dispensed from the following batches: [redacted] ($10cm^2$), [redacted] ($20cm^2$), [redacted] ($30cm^2$), [redacted] ($40cm^2$). For patch sizes $\geq 50cm^2$, the following combinations were used: $50cm^2=20cm^2+30cm^2$, $60cm^2=2x30cm^2$, $70cm^2=30cm^2+40cm^2$, and $80cm^2=2x40cm^2$.

Duration of treatment:

The expected maximum duration of the trial per subject was approximately 1 year.

Reference therapy, dose(s) and mode of administration, batch number(s):

Not applicable

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Criteria for evaluation:

Efficacy:

The primary efficacy variables included the change from Baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) Part III score and in the Parkinson's Disease Sleep Scale (PDSS) score over the course of the trial.

The secondary efficacy variables included the change from Baseline in the Nocturnal Akinesia, Dystonia, and Cramps Score (NADCS) and in the number of nocturias over the course of the trial.

The other variables included the change from Baseline in the Parkinson's Disease Questionnaire (PDQ-8), the UPDRS Part II (Activities of Daily Living) score, the UPDRS Part IV (Complications of Therapy) score, the Beck Depression Inventory (BDI-II), the Parkinson's Disease Non-Motor Symptom Assessment Scale (PDNMS), the Likert Pain Scale, and the total UPDRS Parts II+III score over the course of the trial.

Responder analyses (20%, 25%, and 30% responders) were performed for all UPDRS scores except for UPDRS Part IV.

Safety:

Safety was evaluated by the frequency and severity of adverse events (AEs), as reported spontaneously by the subject or observed by the investigator; by the change in vital signs, body weight, electrocardiograms, and clinical laboratory values; and by changes in physical and neurological examination data over the course of the trial.

Statistical methods:

All statistical efficacy analyses were performed on the Full Analysis Set (FAS) and were descriptive in nature. Safety analyses were based on the Safety Set (SS). 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. Medications were coded using the WHO-DRL dictionary (Version Q2/2004).

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Summary and conclusions:

Subject disposition:

A total of 84 subjects were enrolled in SP915 and comprised the Enrolled Set and the Safety Set. The Full Analysis Set included 83 subjects. Seventy-nine percent of subjects completed the trial. The most common reasons for discontinuation were the incidence of AEs (13%) and withdrawal of consent (6%). One additional subject had 3 AEs leading to withdrawal of the trial medication, but the primary reason for discontinuation was withdrawal of consent. Two percent of subjects were lost to follow-up.

Efficacy results:

The trial data support the following conclusions regarding the efficacy of rotigotine:

Rotigotine shows a long-term efficacy over up to 1 year for the treatment of early-stage and advanced-stage subjects with Parkinson's disease whose dose was titrated to an optimal dose or a maximum dose of up to 16mg/24h.

Based on the results of UPDRS Part III total score, treatment with rotigotine led to a clinically relevant improvement in subjects' motor function over the course of the 1-year trial. Likewise, based on the results of PDSS total score, treatment with rotigotine led to an improvement in subjects' sleep quality.

In addition, all of the other efficacy variables indicate stable improvements in sleep, quality of life, depression, nonmotor symptoms, and pain in this trial.

Safety results:

In this trial, subjects were treated with rotigotine (ranging from 2mg/24h to 16mg/24h) for a mean duration of 321 days (ranging from 42 to 397 days).

Overall, rotigotine was well tolerated during the trial. Most AEs were consistent with stimulation of dopamine receptors, the use of a transdermal patch, and the clinical picture of the subjects' underlying disease. The majority of TEAEs were mild or moderate in intensity and had resolved at the end of the trial. The most common TEAEs were application and instillation site reactions (HLT), somnolence, hallucination, nausea, fall, dizziness, and dyskinesia. Given the comorbidity and the age of the subjects as well as the duration of the trial, the spectrum of TEAEs during this trial was not unexpected.

Fourteen percent of subjects withdrew from the trial due to an AE. The most common TEAEs leading to discontinuation were application and instillation site reactions (HLT) and oedema peripheral. Nineteen percent of subjects reported at least 1 serious AE. Serious

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AEs occurred across multiple SOCs with no obvious grouping or trend.

One death in a subject with a history of diabetes and cardiovascular disease was reported during the Maintenance Period. The PT was death (HLT was death and sudden death). The investigator assessed the death as unlikely related to the intake of trial medication.

Twenty-four percent of subjects reported at least 1 treatment-emergent application and instillation site reaction during the trial. Three of these were severe in intensity and 1 application and instillation site reaction was considered serious in nature. Five subjects discontinued due to application and instillation site reactions.

In general, hematology, clinical chemistry, and urinalysis parameters remained within the normal ranges. Findings related to laboratory parameters reported as TEAEs were reported in ≤3 subjects per AE and showed no obvious grouping.

Overall, there were no clinically relevant changes or trends in the mean changes of vital signs from Baseline to the End of Maintenance for SBP, DBP, or pulse rate.

There was no indication for rotigotine to cause any ECG abnormalities or changes in this trial. Overall, the majority of subjects across all visits had a QTcB or QTcF classified as <450ms at the End of Maintenance (QTcB and QTcF: 91% each) and also had a change from Baseline <30ms (QTcB: 87%; QTcF: 89%) across all visits. Percentages remained stable during the course of the trial.

Conclusions:

Over the course of this 1-year OL trial, rotigotine, given at an optimal dose between 2mg/24h and 16mg/24h, led to long-term improvements in motor function and sleep in subjects with early-stage and advanced-stage idiopathic Parkinson's disease.

Further efficacy results indicate long-term improvements in sleep, quality of life, depression, nonmotor symptoms, and pain in this trial.

Rotigotine was generally well tolerated when up-titrated to 16mg/24h in subjects with early-stage or advanced-stage idiopathic Parkinson's disease.

The most commonly reported TEAEs were application and instillation site reactions, somnolence, hallucination, nausea, fall, dizziness, and dyskinesia. Treatment-emergent AEs are consistent with the previously reported AE profile for rotigotine.

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