SP0977, 2011-000053-23

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 BIOSCIENCES GmbH

Alfred-Nobel-Str. 10

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Official study title:

Multicenter, double-blind, placebo-controlled, two-arm, randomized, parallel, treatment intervention, sleep lab Phase 4 study to assess the effect of rotigotine on nocturnal blood pressure in patients with idiopathic Restless Legs Syndrome

CLINICAL STUDY REPORT SYNOPSIS: SP0977

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: Multicenter, double-blind, placebo-controlled, 2-arm, randomized, parallel, treatment intervention, sleep lab Phase 4 study to assess the effect of rotigotine on nocturnal blood pressure in patients with idiopathic Restless Legs Syndrome

Encore: effects of Neupro on cardiovascular observations in patients with Restless Legs Syndrome

Investigator(s): This was a multicenter study with a total of 9 investigators.

Study site(s): This was a multicenter study with subjects enrolling at 9 centers in [redacted].

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

Studied period: Approximately 9 months
First subject enrolled: 29 Sep 2011
Last subject completed: 21 Jun 2012

Phase of development: Phase 4

Objective(s): The primary objective was to demonstrate that rotigotine decreases the number of elevations of nocturnal blood pressure (BP) associated with periodic limb movements (PLMs) in patients diagnosed with idiopathic Restless Legs Syndrome (RLS).

The secondary objectives were to examine the effects of rotigotine on the total number of elevations of nocturnal BP, on standard measures of cardiovascular (CV) risk surrogate markers, on standard RLS measures of disease severity, and on quality of life measurements.

Methodology: This was a Phase 4, double-blind, randomized, placebo-controlled, 2-arm, parallel-group, multicenter, sleep lab study to evaluate the effect of rotigotine on nocturnal BP elevations with and without associations to PLMs in subjects diagnosed with idiopathic RLS. The study consisted of a Screening Period (1 to 14 days), a Titration Period (maximum 21 days [+3 days]), a Maintenance Period (MP; 28 days), a De-Escalation/Taper Period (hereafter referred to as the Taper Period; 7 days), and a Safety Follow-up (SFU) Period (28 days). Subjects were randomized in a 1:1 ratio to rotigotine or placebo, respectively, using an Interactive Voice Response System with strata defined by the antihypertensive comedication use (concomitant antihypertensive use vs no concomitant antihypertensive use) at the Baseline Visit (Visit 2); a minimum number of subjects randomized per stratum was not required for this study. After randomization at Baseline, subjects' doses were up-titrated to their optimal dose of rotigotine starting at 1mg/24h, with a maximum dose of rotigotine 3mg/24h. Sleep lab measurements were performed in the 2 consecutive nights prior to Baseline (Visit 2) and prior to

*Approved as Neupro® (this note was added for clarification purposes afterwards)

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the End of Maintenance (Visit 7).

Number of subjects (planned and analyzed): A total of 72 subjects were planned to be randomized into SP0977, so that an estimated 60 subjects would complete the study (30 subjects per treatment group). A total of 81 subjects were randomized, with 40 subjects receiving treatment in the placebo group and 40 subjects receiving treatment in the rotigotine group. One subject randomized to the placebo group withdrew consent prior to receiving study medication.

Diagnosis and main criteria for inclusion: Male and female subjects who were ≥18 and ≤75 years of age were included in SP0977. The subjects must have met the diagnosis of idiopathic RLS based on the 4 essential clinical features according to the International Restless Legs Syndrome Study Group. In addition they must have had:

- A score of ≥11 on the RLS-Diagnostic Index (RLS-DI)
- An initial response to previous dopaminergic treatment for RLS or had no previous dopaminergic treatment (ie, de novo)
- A score of ≥15 on the International Restless Legs Syndrome Study Group Rating Scale (IRLS®) (indicating moderate to severe RLS)
- A score of ≥4 points on the Clinical Global Impressions (CGI) Item 1 assessment (indicating moderately ill)
- A score of ≥15 PLM/h on the Periodic Limb Movements Index (PLMI) based on polysomnography (PSG) (recorded during the second night) as assessed by the investigator.

Test product, dose(s) and mode of administration, batch number(s): Rotigotine was provided in silicone-based transdermal patches containing rotigotine formulated in an adhesive matrix. Three different patch sizes were used: 5cm^2, 10cm^2, or 15cm^2. The rotigotine patches contained either rotigotine 2.25mg, 4.5mg, or 6.75mg with a nominal release of 1mg/24h, 2mg/24h, or 3mg/24h, respectively. The following batch numbers were used during the study: [redacted].

Duration of treatment: For all subjects, the study duration was a maximum of 14 weeks.

Reference therapy, dose(s) and mode of administration, batch number(s): Matching placebo patches were administered transdermally with a silicone-based patch. Three different patch sizes were used: 5cm^2, 10cm^2, or 15cm^2. The following batch numbers were used during the study: [redacted].

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Criteria for evaluation:

Efficacy: The primary efficacy variable was:

- Change from Baseline to the end of the 4-week MP in the number of elevations of systolic BP (SBP) during the night that were associated with PLMs

The secondary efficacy variables were:

- Change from Baseline to the end of the 4-week MP in the total number of elevations of SBP during the night
- Change from Baseline to the end of the 4-week MP in the PLMI
- Change from Baseline to the end of the 4-week MP in the IRLS
- Change from Baseline to the end of the 4-week MP in Restless Legs Syndrome-Quality of Life (RLS-QoL)
- CGI Item 2 (change of condition) at the end of the 4-week MP
- CGI Item 1 (severity of illness) at the end of the 4-week MP
- CGI Item 3 (therapeutic efficacy) at the end of the 4-week MP
- Change from Baseline to the end of the 4-week MP in Restless Legs Syndrome-6 Rating Scales (RLS-6)

The other efficacy variables were:

- Change from Baseline to the end of the 4-week MP in the number of elevations of diastolic BP (DBP) during the night that were associated with PLMs
- Change from Baseline to the end of the 4-week MP in the total number of elevations of DBP during the night
- Change from Baseline to the end of the 4-week MP in mean DBP during the night
- Change from Baseline to the end of the 4-week MP in mean SBP during the night
- Change from Baseline in SBP (area under the curve [AUC]) during nocturnal elevations at the end of the 4-week MP
- Change from Baseline in DBP (AUC) during nocturnal elevations at the end of the 4-week MP

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- Change from Baseline in SBP (AUC) during nocturnal elevations associated with PLMs at the end of the 4-week MP
- Change from Baseline in DBP (AUC) during nocturnal elevations associated with PLMs at the end of the 4-week MP
- Change from Baseline to the end of the 4-week MP in mean heart rate (HR) during the night
- Change from Baseline to the end of the 4-week MP in mean HR during PLMs
- Change from Baseline to the end of the 4-week MP in HR variability (HRV)
- Change from Baseline to the end of the 4-week MP in total number of HR elevations during the night
- Change from Baseline to the end of the 4-week MP in number of HR elevations associated with PLMs during the night
- Change from Baseline to the end of the 4-week MP in sleep efficiency (%; sleep time/time in bed [TIB])
- Change from Baseline to the end of the 4-week MP in total sleep time (TST) (all sleep epochs within TIB)
- Change from Baseline to the end of the 4-week MP in total time in sleep stages (absolute and relative)
- Change from Baseline to the end of the 4-week MP in sleep onset latency (time until first sleep stage 2)

The following other efficacy variables were not prespecified in the protocol but were added via the Statistical Analysis Plan (SAP):

<u>PLMI:</u>

- Change from Baseline to the end of the 4-week MP in the PLMI with SBP elevations ($PLMI_{SBPE}$)
- Change from Baseline to the end of the 4-week MP in the PLMI without SBP elevations ($PLMI_{NSBPE}$)
- Change from Baseline to the end of the 4-week MP in the PLMI with DBP elevations ($PLMI_{DBPE}$)

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- Change from Baseline to the end of the 4-week MP in the PLMI without DBP elevations ($PLMI_{NDBPE}$)

Blood Pressure Elevation Index (BPEI):

- Change from Baseline to the end of the 4-week MP in the Systolic Blood Pressure Elevation Index (SBPEI)
- Change from Baseline to the end of the 4-week MP in the Systolic Blood Pressure Elevation Index with PLM ($SBPEI_{PLM}$)
- Change from Baseline to the end of the 4-week MP in the Systolic Blood Pressure Elevation Index without PLM ($SBPEI_{NPLM}$)
- Change from Baseline to the end of the 4-week MP in the Diastolic Blood Pressure Elevation Index (DBPEI)
- Change from Baseline to the end of the 4-week MP in the Diastolic Blood Pressure Elevation Index with PLM ($DBPEI_{PLM}$)
- Change from Baseline to the end of the 4-week MP in the Diastolic Blood Pressure Elevation Index without PLM ($DBPEI_{NPLM}$)

BP and HR changes before and after PLM

- Mean change in SBP from Baseline value for each heartbeat for the duration of 10 beats before and 15 beats after a PLM over all PLMs
- Mean maximum change in SBP from Baseline value over the duration of 10 beats before and 15 beats after a PLM over all PLMs
- Mean change in DBP from Baseline value for each heartbeat for the duration of 10 beats before and 15 beats after a PLM over all PLM
- Mean maximum change in DBP from Baseline value over the duration of 10 beats before and 15 beats after a PLM over all PLMs
- Mean change in HR from Baseline value for each heartbeat for the duration of the 10 beats before and the 15 beats after a PLM over all PLMs
- Mean maximum change in HR from Baseline value over the duration of 10 beats before and 15 beats after a PLM over all PLMs

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Global Subject Rating

- The end of the 4-week MP tolerability rating
- The end of the 4-week MP efficacy

Safety: The following safety variables were assessed:

- Occurrence of adverse events (AEs) reported spontaneously by the subject or observed by the investigator
- Vital signs
- 12-lead electrocardiograms (ECGs)
- Physical and neurological examinations
- Weight
- Pregnancy test (for females of childbearing potential)
- Menstrual and sexual function
- CGI Item 4
- Assessment of suicidality

Statistical methods: The difference between rotigotine and placebo on the change from Baseline to the end of the 4-week MP in the number of elevations of SBP during the night that were associated with PLMs was described using a 95% confidence interval (CI) and the p-value for the Full Analysis Set (FAS).

For the primary efficacy variable, descriptive statistics were presented on both the observed and the change from Baseline to the end of the 4-week MP scores for the FAS. In addition, a histogram of the change from Baseline scores, using intervals of approximately 20 on the x-axis, were also produced in order to provide a first impression on the distribution of the data.

The 95% CI and the p-value for the mean difference between treatments on the primary efficacy variable were obtained, for the FAS, from a linear Analysis of Covariance (ANCOVA) model including a fixed effect for treatment, an adjustment for the fixed effect of Baseline antihypertensive use, as well as a covariate for the Baseline number of elevations of SBP during the night that were associated with PLMs. The treatment effect was estimated on the basis of the least squares mean (LSM) of the difference as well as on the 95% CI and the p-value for that

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difference.

Summary and conclusions:

Subject disposition: A total of 81 subjects were randomized in this study at 9 sites in [redacted]. Of the 81 subjects randomized, 40 subjects entered the Titration Period (TP) in each treatment group; 1 subject (Subject [redacted]) was randomized to the placebo group but withdrew consent prior to entering the TP and prior to receiving study medication. A total of 38 subjects (95.0%) in the rotigotine group and 32 subjects (78.0%) in the placebo group completed the TP of the study. Of the subjects completing the TP and entering the MP of the study, 37 subjects (92.5%) in the rotigotine group and 30 subjects (73.2%) in the placebo group completed the MP.

Overall, reasons for discontinuation included lack of efficacy (1 subject [2.5%] in the rotigotine group and 6 subjects [14.6%] in the placebo group), consent withdrawn (1 subject [2.5%] in the rotigotine group and 3 subjects [7.3%] in the placebo group), AE (2 subjects [5.0%] in the rotigotine group and no subjects in the placebo group), and "other" (no subjects in the rotigotine group and 2 subjects [4.9%] in the placebo group). Discontinuation was also evaluated based on subjects' Baseline antihypertensive use; a similar percentage of subjects in the rotigotine and placebo groups discontinued regardless of Baseline antihypertensive use.

Efficacy results:

SP0977 data support the following conclusions regarding the efficacy of rotigotine:

At the end of the 4-week MP, rotigotine treatment led to a statistically significant reduction in the number of nocturnal elevations of SBP associated with PLMs compared with placebo (change from Baseline to the end of the MP: -240.1 for the rotigotine group, -73.1 for the placebo group; LS mean treatment difference: -160.34; $p<0.0001$).

This reduction was supported by subgroup analyses (antihypertensive use at Baseline, sex, and age), with the exception of the ≥65 years of age subgroup, as well as by analyses of optimal dose, by site, and of the PPS.

The secondary efficacy results indicate that rotigotine treatment led to an improvement compared with placebo in total number of elevations of nocturnal BP, standard measures of CV risk surrogate markers, standard RLS measures of disease severity, and quality of life measurements in subjects with idiopathic RLS.

For the IRLS rating scale total score, a greater improvement was observed in the rotigotine group compared with the placebo group, with a clinically relevant treatment difference (LS Mean: -6.53) between the rotigotine and placebo groups at the end of the MP based on ANCOVA analysis.

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Based on analysis of a number of other efficacy variables, improvements were also observed in the number of nocturnal elevations of DBP (overall and associated with PLMs), in mean reduction in AUC of nocturnal elevations of DBP (overall and associated with PLMs), in mean total number of nocturnal HR elevations associated with PLMs, in PLMI (with and without SBP and DBP elevations), and in SBPEI and DBPEI (overall and for SBPEI associated with PLMs).

Rotigotine treatment was generally similar compared with placebo, on mean changes in nocturnal SBP and DBP, mean reduction in AUC of nocturnal elevations in SBP (overall and associated with PLMs), mean nocturnal HR (overall and associated with PLMs), mean changes in HRV parameters, mean total number of nocturnal HR elevations overall, and mean and maximum change from PLM-Baseline in SBP, DBP, and HR before and after PLMs at Visit 2 and Visit 7.

Changes in sleep efficiency and total sleep time, overall and for the 4 stages of sleep, were similar between the treatment groups. Changes in sleep onset latency also were similar between treatment groups, with the exception of sleep onset latency for non-REM 3 sleep, which was improved in the rotigotine group compared with the placebo group; however, the small number of subjects should be considered when interpreting these results.

At the end of the MP, the majority of subjects in both the rotigotine and placebo groups reported tolerability of the study medication as ‘very good’ or ‘good’. A greater percentage of subjects in the rotigotine group rated study medication efficacy at the end of the MP as ‘very good’ compared with subjects in the placebo group.

Safety results:

In this double-blind, randomized, placebo-controlled study, subjects were up-titrated to their optimal dose of rotigotine (1mg/24h to 3mg/24h) or matching placebo and maintained over the 4-week MP. Overall mean duration of exposure to study medication was 51.8 days (rotigotine) and 47.1 days (placebo).

The majority of TEAEs were consistent with stimulation of dopamine receptors, the use of a transdermal patch, and the subjects’ underlying disease, and were mild or moderate in intensity.

A similar percentage of subjects in both treatment groups reported at least 1 TEAE during the study, with nausea being the most frequently reported TEAE in the rotigotine group and headache being the most frequently reported TEAE in the placebo group.

A similar percentage of subjects in both treatment groups reported TEAEs judged to be related to study medication by the investigator.

Due to the small sample size in individual subgroups, it is difficult to draw any meaningful conclusions.

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There was no clear dose-related pattern for any of the TEAEs reported. The incidence of TEAEs was higher during the TP compared with the MP and the Taper Period, but was similar between treatment groups during each study period.

There were no deaths or treatment-emergent SAEs during the study, and only 2 subjects (both in the rotigotine group) discontinued the study due to TEAEs.

No other significant AEs or pregnancies were reported during the study, and no clinical laboratory measurements were performed. One subject in the rotigotine group reported suicidal ideation at Visit 2, which was reported as a TEAE.

Overall, there were no clinically relevant changes or trends in the mean changes of vital signs from Baseline for SBP, DBP, or pulse rate for either treatment group. Incidences of abnormal SBP and DBP were generally similar in both treatment groups. No TEAEs related to changes in vital signs were reported in either treatment group.

Overall, there was no clinically relevant change in SBP or DBP after standing up. The percentage of subjects meeting orthostatic hypotension criteria was similar between the treatment groups at all assessments and no subjects in either treatment group had a symptomatic persistent drop in blood pressure, as assessed by the investigator.

There were no clinically significant abnormal physical examination findings or neurological examination findings for any subject in either treatment group. No abnormal, clinically significant 12-lead ECG findings were reported for either treatment group at any scheduled or unscheduled study visit.

Conclusions: In this double-blind, placebo-controlled study, rotigotine, given at an optimal dose of 1mg/24h to 3mg/24h, led to statistically significant improvement in the number of nocturnal elevations in SBP associated with PLMs in subjects with idiopathic RLS. In addition, for IRLS rating scale total score, there was a clinically relevant difference between the rotigotine and placebo groups at the end of the MP.

The secondary efficacy results indicate that rotigotine treatment also led to a reduction in total number of elevations of nocturnal BP, as well as improvement in standard measures of CV risk surrogate markers, standard RLS measures of disease severity, and quality of life measurements in subjects with idiopathic RLS.

Treatment-emergent AEs were consistent with stimulation of dopamine receptors, the use of a transdermal patch, and the clinical picture of the subjects' underlying disease, and were consistent with the previously reported AE profile for rotigotine.

Report date: 03 Jun 2013