SP0879, 2006-001937-17

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.

Sponsor:

UCB BIOSCIENCES GmbH

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Proof-Of-Concept Trial To Assess The Efficacy, Safety And Tolerability Of Ascending Doses Of Rotigotine Nasal Spray For The Acute Treatment Of Restless Legs Syndrome (RLS) Symptoms In Subjects With Idiopathic Restless Legs Syndrome

Name of company: SCHWARZ BIOSCIENCES GmbH	**Individual trial table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of finished product: Rotigotine *	**Volume:** Not applicable	
Name of active ingredient: Rotigotine-HCl	**Page:** Not applicable	

Title of trial: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Proof-Of-Concept Trial To Assess The Efficacy, Safety And Tolerability Of Ascending Doses Of Rotigotine Nasal Spray For The Acute Treatment Of Restless Legs Syndrome (RLS) Symptoms In Subjects With Idiopathic Restless Legs Syndrome

Investigators: [redacted], MD; [redacted], MD

Trial site(s): [redacted]

Publication (reference): None at the time of this report

Studied period (years): First subject enrolled: 30Aug2006 Last subject completed: 29Nov2006	**Phase of development: 2a**

Objectives: The objective of this trial was to assess the efficacy of the rotigotine nasal spray in ascending doses in subjects with idiopathic Restless Legs Syndrome. In addition, safety and tolerability, pharmacokinetics and the correlation between efficacy parameters and rotigotine plasma concentration were investigated.

Methodology: This trial was performed in a randomized, double-blind, placebo-controlled, 2-arm parallel group design in 40 male and female subjects with idiopathic RLS, who were L-dopa responders and who were on L-dopa treatment prior to the start of the trial.

Subjects were randomized in a 3:1 ratio to receive escalating doses of rotigotine nasal spray solution (placebo, 62µg, 124µg, and 247µg rotigotine) or matching placebo solution once daily in the afternoon on 4 consecutive days. Subjects randomized to receive rotigotine nasal spray received a single delivery of rotigotine nasal spray or matching placebo in a randomized order on treatment Days 1 or 2 and a single delivery of rotigotine nasal spray in escalating doses on Day 3 and 4.

Number of subjects (planned and analyzed): 40 planned; 59 screened; 44 randomized

Diagnosis and main criteria for inclusion: Male and female subjects with idiopathic RLS, who were on treatment with L-dopa; 18 to 65 years of age.

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

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Test product, dose and mode of administration, batch number: Rotigotine nasal spray; Rotigotine-HCl 2.5mg/mL with 110µL/ delivery or 1.25mg/mL with 110µL/ delivery or 1.25mg/mL with 55µL/ delivery. SCHWARZ PCD and bulk product batch numbers: ND 1421 (2.5mg/mL), batch number: [redacted] ND 1707 (1.25mg/mL), batch number: [redacted] ND 1701 (1.25mg/mL), batch number: [redacted]

Duration of treatment: 4 days.

Reference therapy, dose and mode of administration, batch number: Placebo nasal spray; nasal spray solution identical in appearance to active nasal spray solution. Schwarz PCD number: ND 1704 (110µL/ delivery) or ND 1708 (55µL/ delivery). SCHWARZ PCD and bulk product batch numbers: ND 1704 (110µL/delivery), batch number: [redacted] ND 1708 (55µL/delivery), batch number: [redacted]

Criteria for evaluation:

Efficacy:

Primary variables:

- Severity of RLS symptoms in the legs (sensory symptoms); subjects were asked to rate the severity of the RLS symptoms at the start of each pre dose and post dose Suggested Immobilization Test (SIT-0 to SIT-6) and every 5 minutes during each SIT, using a numeric symptoms severity scale
- Periodic Leg Movement during Wakefulness Index for each SIT and for specified time sections of each SIT (PLMWI, PLM during awake epochs/hour, motor symptoms) was evaluated based on PLM measurements by means of actigraphy, recorded over the entire duration of the SIT period (pre dose and post dose SIT-0 to SIT-6)

Secondary variables:

- Time to premature interruption of a single SIT
- Total time under SIT conditions in the post dose period

Safety:

- Subjective tolerability, adverse events
- Changes in laboratory parameters, vital signs (pulse rate, blood pressure, orthostatic regulation), ECG, and physical examination

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Pharmacokinetics/pharmacodynamics:

Pharmacokinetics:

- Plasma concentration-time profile of rotigotine
- Primary target parameters for Days 1 to 4: $AUC_{(0\text{-}tz)}$, C_{max} of rotigotine
- Secondary target parameters for Days 1 to 4: t_{max}, $t_{1/2}$, $AUC_{(0\text{-}tz),norm}$, $AUC_{(0\text{-}\infty)}$, $AUC_{(0\text{-}\infty),norm}$, $C_{max,norm}$ of rotigotine

PK/PD modeling:

- Correlation between primary efficacy parameters and rotigotine plasma concentration

Statistical methods:

Sample size:

Due to the exploratory nature of this trial, the sample size for this trial was not based on formal statistical calculations. A sample size of 40 subjects was considered to be sufficient to evaluate the primary trial objectives. In the event of drop-out at Day 1 or at Day 2, subjects were to be replaced. Therefore, the actual sample size for this trial could be larger than 40 subjects.

Definition of analysis sets:

The Screened Set includes all subjects who signed an informed consent form and who have data for any eligibility assessment. The Screened Set is the primary analysis set for subject disposition tables and all subject data listings.

The Safety Set (SS), defined as all subjects who received at least 1 delivery of trial medication, was used for the analysis of safety data. An as-treated approach was used for subjects in the SS. The SS is the primary analysis set for safety variables.

The Full Analysis Set (FAS) is the primary analysis set for efficacy in all statistical analyses. The FAS includes all subjects in the SS with at least 1 post dose measurement, analyzed according to the intention-to-treat principle.

The Per Protocol Set includes subjects from FAS without any major protocol deviations.

The Pharmacokinetic Set (PKS), consisting of all subjects belonging to the SS with at least 1 positive (>0) rotigotine concentration value, was used for the analysis of PK data.

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Analysis of primary variables:

The numeric symptoms severity scale was summarized with descriptive statistics and displayed graphically by treatment group, by dose (rotigotine treatment group) or by day (placebo treatment group), by SIT, and by time point within SIT. Baseline-adjusted values (eg, actual numeric symptoms severity scale value minus last pre dose value from SIT-0) were summarized in a similar manner. In addition, within each SIT and across the entire day the average value, minimum and maximum values, and modal value will be computed for each subject. These values were summarized with descriptive statistics by treatment group, by dose or by day, and by SIT.

Within-subject changes were computed as the difference between values at each time point on each of the rotigotine doses to the values at the same time point while on placebo. For the placebo treatment group, Day 1 values serve as the reference point.

PLMWI values were summarized with descriptive statistics and displayed graphically by treatment group, by dose or by day, by SIT, and by time point within each SIT. PLMWI values were generated from time intervals of varying width (eg, 5 minutes, 10 minutes, 15 minutes, for the duration of a SIT, or for the entire post dose period in a day). A separate summary was generated for each measurement interval. Baseline-adjusted values were computed as actual PLMWI value minus the PLMWI value based on all data from SIT-0. Within-subject changes were computed in a similar manner as described for the numeric severity symptoms scale.

Summary and conclusions:

Efficacy: Administration of rotigotine nasal spray in doses of 124µg and 247µg led to a dose-dependent improvement of symptom severity that was visible beginning as early as 10 minutes after the treatment administration (during SIT-1). This dose-dependent effect continued during SIT-2 through SIT-6 until the end of the 4-hour test period. In general, the effect observed following the 2 highest doses was a decrease of approximately 2 points in the average severity scores by SIT. The effect of the lowest rotigotine dose (62µg) on the average severity of symptoms per SIT was similar to the effect observed following placebo treatment. The maximum mean reduction from Baseline in severity scores on each treatment day in the Rotigotine Group were as follows: -0.9 points with placebo; -0.8 points with rotigotine 62µg; -2.0 points with rotigotine 124µg; and -2.3 points with rotigotine 247µg.

An improvement in the PLMWI was observed when subjects were treated with the highest

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rotigotine dose (247µg). In general, the effect observed following this treatment was a decrease from Baseline of >10 points in the PLMWI (from 25.8 during SIT-0 to 13.5 during SIT-2). The results for the 2 lower rotigotine doses (62µg and 124µg) were similar to placebo treatment. PLMWI results for small time intervals such as 5, 10, or 15 minutes are difficult to interpret due to a high level of variability; in most cases, the standard deviations exceeded the mean values.

Most subjects did not require premature interruption of a SIT. The mean total time under SIT conditions in the Rotigotine Group ranged from 187.6 minutes for placebo to 189.2 minutes for 124µg.

Pharmacokinetics/pharmacodynamics results:

A clear dose-dependency was noted for C_{max}, $AUC_{(0-tz)}$, and $AUC_{(0-\infty)}$. Normalizing these parameters by body weight and dose ($C_{max,norm}$, $AUC_{(0-tz),norm}$, and $AUC_{(0-\infty),norm}$) indicated dose-proportionality for the 3 doses.

The difference in the calculated terminal half-life for the lowest rotigotine dose (62µg) compared to the 2 highest rotigotine doses (124µg and 247µg) may be caused by different time intervals for calculation of the terminal half-life (up to 2 hours after administration for 62µg and up to 4 hours for the other doses).

$AUC_{(0-\infty)}$ and $AUC_{(0-\infty),norm}$ values were somewhat lower than expected after treatment with 62µg rotigotine. This may be due to the differences in terminal half-life noted above. Because the extrapolated AUC is greater than 20%, all data for $AUC_{(0-\infty)}$ and $AUC_{(0-\infty),norm}$ values are only rough estimates.

The results from the ANOVA showed point estimates with little or no differences among the 3 dose groups for $C_{max,norm}$, $AUC_{(0-tz),norm}$, or $AUC_{(0-\infty),norm}$. Except for the comparison of $AUC_{(0-\infty),norm}$ values between the 62µg and 247µg rotigotine doses, all comparisons had confidence intervals within the range of 0.7 and 1.43. It should be noted that the $AUC_{(0-\infty)}$ for the 62µg dose group might have been underestimated due to the relatively low plasma concentrations during this treatment.

Safety results:

Nasal application of rotigotine was well-tolerated in this trial. During treatment, the most common TEAEs (reported in ≥2 subjects) were headache, back pain, nausea, dizziness, diarrhea, sleep disorder, and catheter site pain. All TEAEs were mild or moderate in

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intensity and most had resolved by the end of the trial. Additionally, TEAEs occurred with a similar frequency across treatments.

A similar profile was noted when comparing AEs with their onset during rotigotine treatment versus placebo treatment whether in the crossover portion of the Rotigotine Group or in the Placebo Group. There were no SAEs reported during this trial, no subject discontinued from the trial because of an AE, and no subject experienced an AE of special interest (sleep attacks) during the trial. In addition, no laboratory values were reported as drug-related AEs.

Overall, there were no relevant mean changes in ECG parameters during rotigotine treatment at doses up to 247µg/day.

Most subjects had normal vital sign measurements (including orthostatic reaction) and laboratory values (hematology, chemistry, endocrine, and urinalysis) throughout the trial. No subject had a laboratory abnormality that persisted throughout the trial and there were no apparent trends or shifts in laboratory parameters that were of clinical relevance.

Conclusions:

- Administration of rotigotine nasal spray in doses of 124µg and 247µg led to a dose-dependent improvement of sensory RLS symptoms compared with treatment with placebo and 62µg rotigotine, as assessed by subject ratings.
- This dose-dependent improvement was first noted as early as 10 minutes after the treatment administration (during SIT-1) and continued over the 4-hour postdose period.
- Administration of rotigotine nasal spray in a dose of 247µg led to a reduction of RLS motor symptoms as measured by the frequency of periodic leg movements (PLMWI). However, results for the PLMWI for small time intervals such as 5, 10, or 15 minutes should be interpreted with caution due to the high variability observed in this trial.
- Rotigotine plasma concentrations increased very rapidly after nasal spray application and showed a rapid decrease after peak plasma concentration (t_{max} of 10 min), followed by a slower terminal decrease. The 3 doses showed dose-proportional behavior.
- In this trial, nasal application of rotigotine (62, 124, or 247µg/day) was well-tolerated in subjects with RLS.

Final: 27 Jul 2007