SP0873, 2005-004290-19

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.

———————————————————————————————————

Sponsor:

UCB BIOSCIENCES GmbH

(formerly SCHWARZ BIOSCIENCES GmbH)

Alfred-Nobel-Str. 10

40789 Monheim

Germany

Official study title:

A double-blind, placebo-controlled, parallel group, proof of concept trial to assess the tolerability, safety, and efficacy of rotigotine nasal spray for the acute treatment of "off" symptoms in subjects with advanced-stage, idiopathic Parkinson's disease

Name of company: SCHWARZ BIOSCIENCES GmbH	**Individual trial table referring to part of the dossier** Not applicable	*(For National Authority Use Only)*
Name of finished product: Not applicable*	**Volume:** Not applicable	
Name of active ingredient: Rotigotine:	**Page:** Not applicable	
Title of trial: A double-blind, placebo-controlled, parallel group, proof of concept trial to assess the tolerability, safety, and efficacy of rotigotine nasal spray for the acute treatment of "off" symptoms in subjects with advanced-stage, idiopathic Parkinson's disease		
Investigator: Multi-center trial		
Trial sites: This trial was conducted at 18 sites in [redacted].		
Publication (reference): Not applicable		
Studied period (years): First subject enrolled: 08 Feb 2006 Last subject completed: 23 Jun 2006	**Phase of development:** Phase 2	
Objectives: The primary objective of this trial was to assess the tolerability and safety of rotigotine nasal spray in subjects with advanced-stage idiopathic Parkinson disease. The secondary objective was to assess the efficacy of rotigotine nasal spray.		
Methodology: In this double-blind, placebo-controlled, 8-arm trial, 4 groups of subjects received different doses of rotigotine nasal spray, and an additional 4 groups received placebo. Treatment with rotigotine nasal spray consisted of 1 spray actuation of rotigotine in the right or the left nostril (275µg rotigotine hydrochloride in 110µL corresponding to 247µg rotigotine [free base]). In each rotigotine group, 16 subjects were treated with rotigotine nasal spray. The first group received 1 delivery of rotigotine nasal spray, the second group received 2 deliveries (1 in each nostril), the third group received 3 deliveries (1 delivery in 1 nostril and 2 deliveries in the other nostril), and the fourth group received 4 deliveries (2 deliveries in each nostril). Furthermore, 4 groups of 4 subjects received placebo nasal spray (1, 2, 3 or 4 deliveries), resulting in a total of 16 placebo-treated subjects.		
Number of subjects (planned and analyzed): The planned number of subjects to be enrolled was 80. A total of 82 subjects were randomized and treated. All subjects completed the trial.		
Diagnosis and main criteria for inclusion: Subjects were included if they were ≥30 years of age with idiopathic Parkinson's disease of >3 years in duration, as defined by the cardinal sign, bradykinesia, plus the presence of at least 1 of the following: resting tremor, rigidity,		

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

impairment of postural reflexes, and without any known or suspected cause of Parkinsonism. Subjects were expected to be on a stable dose of levodopa, either short-acting or sustained release (in combination with benserazide or carbidopa) for at least 28 days prior to Baseline (Visit 2) of at least 300mg/day, administered in at least 3 intakes. They had a Unified Parkinson Disease Rating Scale (UPDRS) Part III in "off" state of at least 25 points and a Mini Mental State Examination (MMSE) score of ≥25.

Test product, dose and mode of administration, batch number: One to 4 deliveries of rotigotine nasal spray 2.5mg/mL, 275µg rotigotine hydrochloride in 110µL (corresponding to 247µg rotigotine, free base); batch number: [redacted]

Duration of treatment: Each subjects received 1 treatment with 1 to 4 deliveries of rotigotine nasal spray or placebo within 5 minutes.

Reference therapy, dose and mode of administration, batch number: One to 4 deliveries of placebo nasal spray; batch number: [redacted]

Criteria for evaluation:

Safety:

- AEs, as reported spontaneously by the subject or observed by the investigator recorded during the trial
- Changes in blood pressure and heart rate (with special emphasis on potential orthostatic reactions), electrocardiograms, clinical laboratory values
- Changes in physical and neurological examination from Visit 2 to the Safety Follow-up Visit
- Proportion of subjects who complete the trial

Efficacy:

- Change in UPDRS Part III from predose to post-dose
- Change in hand tapping rate from predose to post-dose.
- "Success rate" (percentage of "off" reversals achieved), and the rapidity of "off" reversal

Pharmacokinetics

- Pharmacokinetic (PK) profile and PK parameters (C_{max}, $C_{max,\ norm}$, t_{max}, $t_{1/2}$, AUC(0-t_z), AUC(0-t_z)$_{,\ norm}$, CL/f) of unconjugated rotigotine and total rotigotine

Statistical methods: All statistical analyses were considered exploratory in nature. In general, summary statistics (arithmetic mean, standard deviation, median, minimum, and maximum) for quantitative variables and frequency distributions for qualitative data were presented for each treatment group. Statistical tables, listings and figures present results by treatment group, considering 6 treatment groups. Subjects receiving rotigotine were grouped by the number of deliveries administered (1, 2, 3, or 4 deliveries). All subjects randomized to placebo were combined into a single placebo treatment group, regardless of number of deliveries. Baseline was defined for analysis as the value obtained at Visit 2 (or Visit 1, if Visit 2 was not available). Efficacy analyses assessed the changes from the predose value, which was defined as the value obtained at Visit 3 prior to first delivery of trial medication.

Summary and conclusions:

Safety results:

Subjects were randomized to receive either rotigotine or placebo, administered as nasal spray solution in 1 dose. Subjects in each group received either 1 delivery, 2 deliveries, 3 deliveries or 4 deliveries into the nostrils, corresponding to 0.25mg, 0.49mg, 0.74mg, or 0.99mg of rotigotine free base, or placebo.

Rotigotine nasal spray was well tolerated both systemically and locally. The majority of AEs were mild or moderate in intensity. In total, 43% of subjects (35/82) reported at least 1 AE. A correlation between the incidence of an AE and the dose of rotigotine was not apparent. Most of the common AEs were consistent with stimulation of dopamine receptors and the use of a nasal spray. Treatment-emergent AEs reported with an incidence ≥5% were Application and Instillation Site Reactions ([HLT] 12%), somnolence (11%), dizziness (9%), urinary tract infection (6%), and yawning (5%). All of these AEs except for the events of urinary tract infection and 1 AE of somnolence were assessed as related to trial medication by the investigator.

No death occurred during the trial and there was no discontinuation from the trial due to a treatment-emergent AE. Two treatment-emergent SAEs were reported during the trial, symptomatic bradycardia and depression. The event of depression was assessed as unrelated to trial medication and the event of symptomatic bradycardia as highly probably related to trial medication. Both events resolved.

Other significant AEs that were examined were application site reactions, sleep attacks, cardiac arrhythmias, severe orthostatic hypotension, severe hypotension, hallucinations, events suggestive of falls, syncope, and markedly abnormal laboratory values. Eleven subjects experienced other significant AEs, and 10 of them (12% of subjects) had application and instillation site reactions (High Level Term); all application site reactions were all mild in intensity and resolved. The other significant TEAEs were 1 AE of hypotension (severe in intensity) and 1 AE of sleep attacks (mild in intensity).

There were no apparent trends or shifts in laboratory parameters that were of clinical relevance. Five laboratory abnormalities were reported as AEs (all were abnormal urinalysis results).

No clinically relevant mean changes in vital signs were noted. There was no indication of a relationship between the dose of rotigotine nasal spray and the incidence of orthostatic hypotension. One subject had severe hypotension postdose. The overall incidence of symptomatic orthostatic hypotension was low as indicated by the small number of AEs associated to this condition.

The same subject that experienced the SAE of symptomatic bradycardia, and the AE of severe hypotension had a postbaseline QTcF interval ≥500msec and QTcB interval ≥500msec, representing a change from Baseline of ≥60msec for both parameters. No other relevant changes or shifts in ECG parameter were seen.

Efficacy:

There was no clinically sufficient difference between placebo and rotigotine treatment in the mean change from Baseline in UPDRS Part III at the most relevant time point (24 min post-dose).

Pharmacokinetic results

Rotigotine was rapidly absorbed after nasal spray administration and C_{max} was reached after approximately 8 minutes postdose. There was a consistent correlation of dose and mean plasma concentration between the dose groups, and the results from the ANOVA of derived PK parameters were supportive of a positive correlation between bioavailability and dose.

For unconjugated rotigotine, mean $C_{max, norm}$.ranged from 23.981ng/mL*kg (lowest dose group) to 195.434ng/mL*kg (highest dose group), and mean $AUC_{(0-tz), norm}$ ranged from 30.593ng/mL*h*kg (lowest dose group) to 157.694ng/mL*h*kg (highest dose group).

For total rotigotine, mean $C_{max, norm}$.ranged from 243.175ng/mL*kg to 949.859ng/mL*kg, and mean $AUC_{(0-tz), norm}$ ranged from 349.892ng/mL*h*kg to 1287.10 ng/mL*h*kg. The log linear illustrations of plasma concentrations show the same rate of elimination for all 4 dose groups.

Conclusions:

- Rotigotine nasal spray was well tolerated both systemically and locally.
- The most common AEs were consistent with stimulation of dopamine receptors and the use of a nasal spray.
- No new safety concerns did arise from this trial.

The application of the rotigotine nasal spray at a single dose up to 0.99mg rotigotine did not improve motor function relevantly better than placebo in a time window up to 30 minutes post dose in subjects with advanced-stage Parkinson disease who were in the "off" state.

Date of the report: 05 Feb 2008