SP0512

CLINICAL STUDY REPORT SYNOPSIS

Sponsor:

UCB Biosciences, Inc.

(formerly: Schwarz Biosciences, Inc.)

8010 Arco Corporate Drive

Raleigh, North Carolina 27617

United States of America

Official study title:

A multi-center, multinational, phase III, randomized, double-blind, placebo-controlled trial, of the efficacy and safety of the rotigotine patch in subjects with early-stage, idiopathic Parkinson's disease (Part 1)

Name of Company: Schwarz Biosciences	**Individual Study 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 multi-center, multinational, phase III, randomized, double-blind, placebo-controlled trial, of the efficacy and safety of the rotigotine patch in subjects with early-stage, idiopathic Parkinson's disease (Part 1).	
Investigators: Multicenter trial	
Trial site(s): 42 sites in the US and 5 sites in Canada	
Publication (reference): None.	
Studied period (years): **First subject enrolled**: 20 November 2001 **Last subject completed**: 16 April 2003	**Phase of development:** Phase 3
Objectives: The primary objective of this trial was to demonstrate that rotigotine is efficacious in early-stage Parkinson's disease subjects. A secondary objective was to demonstrate the tolerability and safety of rotigotine.	
Methodology: Part 1 of this trial was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-arm, parallel-group trial of rotigotine in subjects with early-stage, idiopathic PD. Rotigotine doses included 4.5mg/day, 9.0mg/day, and 13.5mg/day. Trial periods consisted of a 4-week pre-treatment (washout) period, a 3-week dose escalation period, a 24-week dose maintenance period, and a 4-week follow-up period for a total duration of 38 weeks. Part 2 of this trial is a long-term, open-label extension trial. Results from Part 2 will be reported separately.	
Number of subjects (planned and analyzed): The planned number of subjects was 300 for enrollment, 250 for randomization, and 240 for the primary analysis. A total of 302 subjects were enrolled, 277 were randomized, and 273 were included in the primary efficacy analysis.	
Diagnosis and main criteria for inclusion: Subjects were included if they had been diagnosed with idiopathic Parkinson's disease of ≤5 years in duration, had a Unified Parkinson's Disease Rating Scale (UPDRS) motor score (Part III) of ≥10 at baseline, had a Hoehn & Yahr stage ≤III, and had at least 2 or more of the following cardinal signs: bradykinesia, resting tremor, rigidity, postural instability; and without any other known or suspected cause of Parkinsonism. If the subject had been receiving an anticholinergic agent, an MAO-B inhibitor, an NMDA-antagonist (ie, amantadine), he/she must have been on a	

stable dose for at least 28 days prior to baseline and be maintained on that dose for the duration of the trial. Subjects were excluded from the trial if they had prior or concurrent therapy with a dopamine agonist within 28 days of the baseline visit; if they had prior therapy with carbidopa/levodopa within 28 days of baseline; if the subject had received carbidopa/levodopa for more than 6 months since diagnosis; if the subject had atypical Parkinson's syndrome(s) due to drugs (eg, metoclopramide, flunarizine), metabolic neurogenetic disorders (eg, Wilson's disease), encephalitis, cerebrovascular disease or degenerative disease (eg, progressive supranuclear palsy); or if the subject had a history of pallidotomy, thalamotomy, deep brain stimulation or fetal tissue transplant.

Test product, dose and mode of administration, batch number:

$10cm^2$, $20cm^2$, and $30cm^2$ rotigotine transdermal patches corresponding to 4.5mg, 9.0mg, and 13.5mg rotigotine, respectively. Initial doses were 4.5mg/day with weekly increases of 4.5mg/day to a maximum target dose of 13.5mg/day. Batch numbers used were WE11682, 2010618370, 2020318300 (for the $10cm^2$ patches), WE11683, 2010718440, 2020318240 (for the $20cm^2$ patches), and WE11684, 2010618360, 2020318370 (for the $30cm^2$ patches).

Duration of treatment: 27 weeks (3 weeks dose escalation, 24 weeks dose maintenance).

Reference therapy, dose and mode of administration, batch number:

$10cm^2$, $20cm^2$, and $30cm^2$ matching placebo transdermal patches containing 0mg rotigotine. Placebo-treated subjects underwent a sham titration which matched the titration schedule for the rotigotine-treated subjects. Batch numbers used were WE11738 and 2020318210 (for the $10cm^2$ patches), WE11739 and 2020318200 (for the $20cm^2$ patches), and 2010618340 and 2020318170 (for the $30cm^2$ patches).

Criteria for evaluation:

Efficacy: For the United States (US), efficacy was determined by the change in the sum of scores from the Activities of Daily Living (ADL) and the Motor Examination sections in the UPDRS (parts II+III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase. For the European Union (EU), efficacy was determined by the subject's response to therapy. A "responder" was a subject with a 20% or greater decrease in the sum of scores from the ADL and Motor Examination sections in the UPDRS (parts II+III: a UPDRS subtotal) from the baseline visit to the end of the double-blind maintenance phase.

Secondary efficacy variables for both the US and EU included: percent change in the UPDRS subtotal (parts II+III) from the baseline visit to the end of the double-blind maintenance phase; change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part II; change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part III; area under the curve for the change from baseline values of the UPDRS subtotal (parts II+III) during the double-blind maintenance phase. In addition, the primary variable for the US was a secondary variable for the EU, and vice versa.

Pharmacokinetics: The plasma levels of rotigotine were measured. Population pharmacokinetics analyses were performed to test whether the factors gender, age, bodyweight, creatinine clearance, and liver enzymes are possible covariates to explain the variability of pharmacokinetic parameters within this population.
Safety: Safety was assessed by summary of the following: • Adverse events, as reported spontaneously by the subject or observed by the investigator recorded during the double-blind part of the trial. • Changes in the vital signs, body weight, electrocardiograms, and clinical laboratory values during the double-blind part of the trial. • Changes in the physical and neurological examination data during the double-blind part of the trial. • Subjects who complete the double-blind maintenance phase of the trial.
Other assessments: Change from the baseline visit to end of the double-blind maintenance phase in Clinical Global Impressions; change from the pre-treatment visit to end of the double-blind maintenance phase in Hoehn and Yahr stage; change in quality of life, from the baseline visit to the end of the double-blind maintenance phase, as assessed using the EuroQol EQ-5D scoring system; change from the baseline visit to the end of the double-blind maintenance phase in Epworth Sleepiness Scale score. Serum prolactin levels were measured.
Statistical methods: For the US, the primary variable on which the efficacy of rotigotine was assessed was the change from baseline (Visit 2) to the end of the maintenance phase (Visit 11) in the value of the sum of scores from parts II and III of the UPDRS. This difference (or change) contains, among other possible effects, the effect due to treatment. An analysis of covariance (ANCOVA) on these observed changes from baseline was used to estimate the mean difference in treatment effect between rotigotine and placebo while adjusting for the geographic region of the subject's assigned investigational center (a blocking factor) and the subject's baseline UPDRS subtotal (a covariate). The investigational hypothesis is that the mean improvement due to rotigotine is greater than that of placebo (ie, the mean change in the UPDRS subtotal for rotigotine treated subjects is a larger negative value than that for placebo treated subjects). For the EU, each subject was classified as a responder (defined as a subject who experienced at least a 20% decrease in their UPDRS Subtotal (Part II+III) from baseline to the end of the maintenance phase) or a non-responder. Each treatment group then has an associated responder rate which is the proportion of subjects responding to treatment. The investigational hypothesis that the proportion of responders is greater for rotigotine-treated subjects than for placebo-treated subjects was tested. Using sample sizes of 160 for rotigotine and 80 for placebo, and an assumed standard deviation of approximately 7 (as seen in a previous trial of rotigotine in early PD, SP506) for the change in the UPDRS subtotal, there would be at least 95% power for the group comparison (placebo vs. rotigotine) anticipating a difference of 4 points. Using a more conservative standard deviation of 10 points, the power is still above 80%. The Full

Analysis Set (for efficacy analyses) included 177 rotigotine-treated and 96 placebo-treated subjects.

Summary and Conclusions:

Efficacy Results:

Rotigotine resulted in improvement in the absolute UPDRS (Parts II+III) subtotal score at the end of treatment (approximately -4 points), whereas the equivalent score in placebo-treated subjects indicated deterioration (+1.3 points). These end of treatment scores are highly statistically significantly different from each other ($p<0.0001$). Rotigotine resulted in a higher proportion of responders at the end of treatment compared with placebo for all of the pre-defined responder groups (ie, 48% vs. 19% for the 20% responder group; 44% vs. 16% for the 25% responder group; and 37% vs. 13% for the 30% responder group). For all categories, these end of treatment responder proportions are highly statistically significantly different from each other ($p<0.0001$). Rotigotine resulted in a greater relative improvement in the UPDRS (Parts II+III) subtotal score at the end of treatment (approximately 15% improvement) compared with the relative change in placebo-treated subjects (approximately 7% deterioration). These end of treatment relative changes are highly statistically significantly different from each other ($p<0.0001$). Among the rotigotine-treated subjects, 91% received 13.5mg/day, 6% received 9.0mg/day and 3% received 4.5mg/day as their maintenance dose.

Rotigotine resulted in a greater area under the curve (AUC) for the UPDRS (Parts II+III) subtotal score at the end of treatment compared with the AUC for placebo-treated subjects. Treatment effects on the other secondary endpoints were supportive of the results obtained for the primary endpoint.

Pharmacokinetics Results:

Mean rotigotine plasma levels measured on Day 8 of the titration period, prior to removal of the 4.5mg patch, were 0.27ng/mL (n=54, median=0.22). Prior to removal of the 9.0mg patch on Day 15 of the titration period, the mean rotigotine plasma levels were 0.51ng/mL (n=51, median=0.44). On Day 1 of the maintenance period, mean rotigotine plasma levels were 0.76ng/mL (n=48, median=0.71) prior to removal of the 13.5mg patch. Plasma levels remained stable throughout the maintenance period.

Safety Results:

- Rotigotine was generally well-tolerated. Most AEs were consistent with stimulation of dopamine receptors and the use of a transdermal delivery system. The AEs were similar between the treatment groups, or were typical of those that occur in this elderly patient population.
- AEs were generally mild or moderate in intensity. Over the entire treatment period, the most common AEs (ie, those having an incidence ≥5%) that occurred more frequently among rotigotine-treated subjects compared with placebo-treated subjects included application site reaction, nausea, somnolence, dizziness, headache, vomiting, insomnia, unspecified accidents, dyspepsia, tremor, constipation, diarrhea, and back pain.
- The only adverse events clearly related to the rotigotine patch and not typical of other

dopamine agonists were application site reactions. These were generally mild, and led to trial discontinuation in 9/79 (11%) of rotigotine-treated subjects who reported the occurrence of application site reaction (ie, 5% (9/181) of all rotigotine-treated subjects). Application site reactions resolved in all subjects who discontinued the trial.

- Sleep attack was reported by 2/181 (1%) rotigotine-treated subjects and no placebo-treated subjects. Both of these events resolved, and both subjects completed the trial.
- The incidence of orthostatic hypotension was similar between treatment groups.
- Hallucinations were not reported among any rotigotine-treated subjects.
- The incidence of edema was similar between treatment groups.
- The incidence of SAEs was higher among rotigotine- versus placebo-treated subjects (7% versus 4%). These occurred across multiple body systems with no obvious trends. In most of the rotigotine-treated subjects, the dose was not changed or interrupted, and the occurrence of an SAE resulted in subject withdrawal in approximately 2% (4/181) of rotigotine-treated subjects. Three percent of rotigotine-treated and 1% of placebo-treated subjects reported SAEs that were judged by the investigator to be related to trial medication.
- A total of 6% (6/95) of placebo-treated subjects and 14% (25/181) of rotigotine-treated subjects reported AEs leading to discontinuation. In the rotigotine group, these AEs occurred across multiple body systems but predominantly included application site reaction (5% [9/181] of all rotigotine-treated subjects). Most of the remaining AEs that lead to discontinuation were typical of those that occur in patients who have PD or who are treated with dopamine agonists.
- Changes in electrocardiogram findings were similar between treatment groups. There was a marginal increase in heart rate with rotigotine treatment which attenuates with time. Generally, there is no difference between rotigotine and placebo treatments in regard to the distribution of QT/QTc relative and absolute values across the defined QT duration categories.
- Taking into account this relatively elderly population, there were no clinically relevant changes in vital signs, laboratory parameters, neurological findings (except UPDRS findings) or physical examination.

Other Results:

- For the CGI, a greater proportion of rotigotine-treated subjects showed some level of improvement compared with subjects who received placebo. A lower proportion of rotigotine-treated subjects were worse compared with placebo-treated subjects.
- A similar proportion of subjects in each treatment group shifted from “not excessively sleepy” at baseline to “excessively sleepy” at the end of the treatment period.
- There was no appreciable change in the Hoehn & Yahr score over the 6-month duration of this trial, indicating little progression in the severity of PD.
- For each of the domains of the EuroQol questionnaire, rotigotine-treated subjects generally experienced a favorable treatment effect compared with placebo-treated subjects. Very few subjects in either treatment group experienced marked deterioration

over the course of this trial. Changes from baseline to the end of treatment in the health state score were small in both treatment groups, but tended to be smaller among rotigotine-treated subjects.

- In the placebo group, the mean serum prolactin levels were between 6.4 and 7.7ng/mL while they were between 4.8 and 5.4ng/mL during the maintenance period after application of the 13.5mg patch. The mean individual change from the baseline value in the placebo group was -0.1ng/mL (n=26, median=0.5ng/mL) while the mean change from baseline in the rotigotine group was -1.9ng/mL (n=51, median=-2.0) on Day 1 after application of the 13.5mg patch. Comparable results were measured throughout the maintenance period.

Conclusions:

- Rotigotine is effective for the treatment of early-stage PD in patients titrated to a target dose of 13.5mg/day.
- The positive treatment effect of rotigotine in early PD is predominantly due to a sustained improvement in motor function (as measured by UPDRS Part III); effects on the activities of daily living (as measured by UPDRS Part II) are of a smaller magnitude.
- In patients with early-stage PD titrated to a target dose of 13.5mg/day, rotigotine plasma levels remain stable over 6 months of treatment.
- The results of the population pharmacokinetic analysis do not suggest that gender, age, body weight, and renal function explain the variability in plasma concentrations of rotigotine.
- As seen in other dopamine agonists, prolactin plasma concentrations decrease after exposure to rotigotine, indicating D_2-receptor agonist activity.
- Generally, rotigotine may be safely administered in patients who have been diagnosed with early-stage PD when titrated to a target dose of 13.5mg/day.
- The dose titration scheme used in the trial was well-tolerated and is, therefore, appropriate for use in patients with early-stage Parkinson's Disease.
- The adverse events seen are generally similar to those attributed to other dopamine agonists.
- Rotigotine is weakly irritating to the skin compared with placebo, but is usually well-tolerated.
- There is no evidence for an association between rotigotine treatment and QTc prolongation.
- The dose de-escalation scheme used in this trial allows a safe and tolerable withdrawal of the drug from subjects.

Date of the report: 5 April 2004