SP0650

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 3, randomized, double-blind, parallel group, placebo-controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced-stage, idiopathic Parkinson's disease who are not well controlled on levodopa (Part 1).

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

Title of trial: A multi-center, multinational, Phase 3, randomized, double-blind, parallel group, placebo-controlled trial of the efficacy and safety of rotigotine CDS patch (2 target doses) in subjects with advanced-stage, idiopathic Parkinson's disease who are not well controlled on levodopa (Part 1).

Investigators: Multi-center trial

Trial sites: 55 sites in the United States (US) and Canada

Publication (reference): None.

Studied period (years): **First subject enrolled**: 19 Dec 2001 **Last subject completed**: 19 Apr 2004	**Phase of development:** Phase 3

Objectives: The primary objective of this trial was to show that rotigotine is efficacious in advanced-stage Parkinson's disease patients as an adjuvant therapy. A secondary objective was to demonstrate the tolerability and safety of rotigotine.

Methodology: SP650 Part 1 was a Phase 3, multi-center, randomized, double-blind, placebo-controlled, 3-arm, parallel-group trial of rotigotine in subjects with advanced-stage idiopathic Parkinson's disease. Rotigotine target doses included 18.0mg/day and 27.0mg/day. The trial consists of a 4-week Pre-treatment period, a Dose-escalation Phase (up to 5 weeks), a 24-week Maintenance Phase, a De-escalation Phase (up to 8 days), and a 4-week Safety Follow-up period for a total of approximately 38 weeks. SP650 Part 2 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 460 for enrollment, 340 for randomization, and 330 for the primary analysis. A total of 462 subjects were enrolled, 351 subjects were randomized, and 341 subjects were included in the primary analysis.

Diagnosis and main criteria for inclusion:

Subjects were included if they were ≥30 years of age with idiopathic Parkinson's disease of >3 years duration as defined by the cardinal Parkinsonian sign of bradykinesia, plus the presence of at least one of the following cardinal features: resting tremor, rigidity, impairment of postural reflexes, and without any other known or suspected cause of Parkinsonism. Subjects were required to be Hoehn & Yahr stage II through IV in both the

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

"on" and "off" states and have a Mini-Mental State Examination (MMSE) score of ≥25. Subject were on a stable dose of L-DOPA of at least 200mg/day (administered in at least 2 daily intakes), either short-acting or sustained release (in combination with benserazide or carbidopa) for at least 28 days prior to Baseline (Visit 2) and were not adequately controlled on a L-DOPA dose that was judged by the treating physician to be optimal. Subjects receiving an anticholinergic agent, a monoamine oxidase B (MAO-B) inhibitor, or an N-methyl-D-aspartate (NMDA) antagonist, were on a stable dose for at least 28 days prior to Baseline and were maintained on that dose for the duration of the trial. Subjects were on stable doses of all anti-Parkinsonian medications for at least 20 days prior to completing the 6 Baseline diaries. Subjects were excluded from the trial if they 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 they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant; were receiving therapy with a dopamine agonist currently or had done so within 28 days prior to Baseline; had received within 28 days prior to the Baseline visit therapy with methylphenidate, amphetamine, or catechol-O-methyl transferase (COMT) inhibitors.

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 9.0mg/day with weekly increases of 4.5mg/day to target doses 18.0 and 27.0mg/day (or lesser optimal dose). Batch numbers used were WE11682, 2010618370, 2020318300 (for the $10cm^2$ patches), WE11683, WE12403, WE12607, 2020318240 (for the $20cm^2$ patches), and WE12292, WE12578, 2010618360, 2020318370 (for the $30cm^2$ patches).

Duration of treatment: 30 weeks (Dose-escalation Phase up to 5 weeks, a Maintenance Phase of 24 weeks, and a De-escalation Phase up to 8 days).

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 that matched the titration schedule for the rotigotine-treated subjects. Batch numbers used were WE11738, 2020318210 (for the $10cm^2$ patches), WE11739, WE12610, 2020318200 (for the $20cm^2$ patches), and WE12632, 2010618340, 2020318170 (for the $30cm^2$ patches).

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

Criteria for evaluation:

Efficacy: For the United States (US), efficacy was determined by the reduction in absolute time spent "off" from Baseline 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 30% or greater decrease in absolute time spent "off" from the Baseline to the end of the double-blind Maintenance Phase. Secondary efficacy variables for both the US and EU included: Change and percent change from Baseline to the end of double-blind Maintenance Phase in absolute and relative time spent "on"; change from Baseline to the end of double-blind Maintenance Phase in the number of "off" periods; change from Baseline to the end of double-blind Maintenance Phase in the status of the subject (on/off) after wake-up; change from Baseline to the end of double-blind Maintenance Phase in Unified Parkinson's Disease Rating Scale (UPDRS) Parts II, III, and IV during "on" periods; and area under the curve (AUC) over the Maintenance Phase for the absolute time spent "off" during the double-blind Maintenance Phase of the trial. In addition, the primary variable for the US was a secondary variable for the EU, and vice versa.

Pharmacokinetics/pharmacodynamics: The plasma levels of rotigotine were measured.

Safety: Safety was assessed by summary of the following:

- Adverse events (AE), as reported spontaneously by the subject or observed by the investigator recorded during the double-blind part of the trial. This included all AEs, serious AEs, dropouts due to AEs, and AEs of special interest.
- Changes in the vital signs, body weight, electrocardiograms, clinical laboratory values, and Epworth Sleepiness Scale scores during the double-blind part of the trial.
- Changes in the physical and neurological examination data during the double-blind part of the trial.
- Percentage of subjects who completed the double-blind Maintenance Phase of the trial.

Other variables: Other variables included: change from baseline to the end of the Maintenance Phase in the EuroQoL EQ-5D (a measure of health status); change from Baseline to the end of the double-blind Maintenance Phase in the Epworth Sleepiness Scale; percentage change from Baseline to the end of the Maintenance Phase in total L-dopa dose; change from Baseline to the end of the Maintenance Phase in duration of sleep; change from Baseline to end of the double-blind Maintenance Phase in Clinical Global Impressions (CGIs); change from Pre-treatment to the end of the double-blind Maintenance

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

Phase in Hoehn & Yahr stage.

Statistical methods: For the US, the primary variable in this trial on which the efficacy of rotigotine was assessed was the change from Baseline to the end of the double-blind Maintenance Phase (Visit 14) in the absolute time spent "off" with "off" defined as the number of hours marked "off" during a 24-hour period on the subject daily diary cards. The change from Baseline values contain, among other possible effects, the effect due to treatment. An analysis of covariance (ANCOVA) on these average absolute "off" times was used to estimate the mean change from Baseline for each treatment arm as well as the difference between the arms while adjusting for the geographic region of the subject's assigned investigational center (a blocking factor) and the subject's Baseline average absolute off-time (a covariate). Higher average absolute off-times correspond to more severe Parkinson's disease state, and because the change from Baseline was calculated as "end of Maintenance Phase - Baseline," a negative change corresponds to an improvement.

For the EU, the primary variable was based on a subject's response to treatment as assessed by the percent change from Baseline to the end of the double-blind Maintenance Phase in the absolute time spent "off." A responder was defined as a subject with a ≥30% decrease in absolute time spent "off." As for the US endpoint, the average absolute time spent "off" was specifically used for analysis (see US section above).

Because this Phase 3 trial also had a dose-response aspect (3 arms), the global null hypothesis was that the mean change from Baseline was the same across the 3 treatment groups.

Summary and conclusions:

Efficacy results: Rotigotine 18.0mg/day and 27.0mg/day decreased the absolute "off" time at the end of treatment (by 2.7 hours and 2.1 hours, respectively) compared with a decrease of 0.9 hour in placebo-treated subjects. These end of treatment decreases in "off" time for both rotigotine treatment groups are statistically significantly different from the decrease in the placebo group ($p<0.001$ for the 18.0mg/day group; $p=0.003$ for the 27.0mg/day group). Rotigotine 18.0mg/day and 27.0mg/day also resulted in higher proportions of subjects who had a ≥30% decrease in the absolute amount of "off" time at the end of treatment (57% and 55%, respectively) compared with placebo (34%). The proportions of responders in both rotigotine treatment groups are statistically significantly different from the proportion of responders in the placebo group ($p<0.001$ for both rotigotine groups).

With regard to secondary efficacy parameters, these analyses show that both the

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

18.0mg/day and 27.0mg/day rotigotine groups:

- reduced the amount of time subjects spent in the "off" state and increased the amount of time subjects spent in the "on" state (without troublesome dyskinesia) in a clinically relevant manner, on both an absolute and relative basis.
- produced larger average decreases in the number of "off" periods (-1.5 and -1.3, respectively) compared with placebo (-0.7).
- produced larger decreases in the proportion of subjects who woke up in the "off" state (-28.8% and -22.6%, respectively) compared with placebo (-9.1%).
- produced larger decreases in the UPDRS Part II and Part III scores at the end of the Maintenance Phase compared with the corresponding changes for the placebo group.
- produced larger decreases in the area under the curve in the time spent "off" during maintenance (-563 and -389, respectively) compared with placebo (-208).

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

Pharmacokinetics/pharmacodynamics results:

- In general, rotigotine plasma levels were similar to those measured in previous trials of subjects with early-stage Parkinson's disease.
- The mean rotigotine plasma levels measured in subjects with advanced-stage Parkinson's disease increased in a dose-proportional manner during the Titration Phase.
- Mean plasma levels remained generally stable throughout the 6 month Maintenance Phase.
- Mean rotigotine plasma levels were similar in subjects <65 years of age or ≥65 years of age.
- Higher mean rotigotine plasma levels were observed in females in the 18.0mg/day group, which may be explained by differences in body weight.

Safety results:

- Rotigotine was generally well-tolerated. Most AEs were consistent with stimulation of dopamine receptors or the use of a transdermal delivery system. The AEs were generally 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 treatment-emergent AEs that occurred more frequently among rotigotine-treated subjects (in either dose group) compared with placebo-treated subjects (in descending frequency) were application and instillation site reactions, somnolence, nausea, dizziness, dyskinesia, edema peripheral, disturbances in initiating and maintaining sleep, perception disturbances, arthralgia, vomiting, headache, constipation, nasopharyngitis, diarrhea, hypertension, nightmare, and balance disorder.
- Compared with the most common AEs reported during titration, the frequencies of nausea, vomiting, constipation, dizziness, dyskinesia, and headache were lower during the Maintenance Phase despite the longer duration of the Maintenance Phase (5 weeks vs 24 weeks). In contrast, the incidence of peripheral edema and fall was higher during the Maintenance Phase. For all other AEs reported with an incidence ≥5%, no obvious trend between Titration and Maintenance Phase was observed.
- The only adverse events clearly related to the rotigotine patch and not typical of other dopamine agonists were application and instillation site reactions which predominantly included erythema, pruritus, dermatitis, and irritation. Nearly all application and instillation site reactions in all treatment groups were mild or moderate in intensity,

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

most resolved by the end of the double-blind treatment period, most did not require a change of dose, and none were reported as an SAE. Application and instillation site reactions led to trial discontinuation in 4% (4/94) of rotigotine-treated subjects who reported the occurrence of application site reaction (ie, 1.7% (4/229) of all rotigotine-treated subjects). In all 4 of these subjects, the reaction resolved.

- Sleep attack was reported by 1 rotigotine-treated subject and no placebo-treated subjects. The subject prematurely discontinued the trial, and the event resolved.
- The incidence of orthostatic hypotension was lower among rotigotine-treated subjects compared with placebo-treated subjects. All events were mild or moderate in intensity and none were reported as an SAE. Two placebo-treated subjects and no rotigotine-treated subjects discontinued the trial because of orthostatic hypotension.
- Perception disturbances (which included hallucination; hallucination, tactile; hallucination, visual; hallucinations, mixed; and illusion) were reported more frequently among the rotigotine-treated subjects compared with placebo-treated subjects. Nearly all were mild or moderate in intensity, and none were reported as an SAE. Six subjects discontinued the trial because of hallucination (1 placebo-treated subject, 5 rotigotine-treated subjects), and the hallucinations resolved in all 6 subjects.
- The incidence of falls and injuries suggestive of falls were similar between treatment groups. A serious fall that resulted in subject discontinuation was reported in 1 rotigotine-treated subject.
- Visual abnormalities were reported by no placebo-treated subjects and by 3 rotigotine-treated subjects. None of these were reported as severe or serious, and none resulted in discontinuation from the trial.
- Two deaths were reported among rotigotine-treated subjects (cerebrovascular accident [stroke] in 1 subject, and unexplained death [but consistent with cardiac pump failure] in another subject. The investigator judged the stroke to have an unlikely relationship to trial medication and the unexplained death to be unrelated to trial medication. There were 2 deaths in the placebo group.
- The incidence of SAEs was similar among treatment groups (7%-10% in rotigotine-treated subjects versus 8% in placebo-treated subjects). These occurred across multiple system organ classes with no obvious trends. The occurrence of an SAE resulted in subject withdrawal in 2.6% (6/229) of rotigotine-treated subjects. Approximately 2% of rotigotine-treated and 1% of placebo-treated subjects reported SAEs that were judged by the investigator to be related to trial medication.

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

- A total of 8% (10/120) of placebo-treated subjects and 16% (36/229) of rotigotine-treated subjects reported AEs leading to discontinuation. Among the rotigotine-treated subjects, these AEs occurred across multiple system organ classes which mainly included nervous system disorders, gastrointestinal disorders, general disorders and administration site conditions, and psychiatric disorders. Most of these AEs were typical of those that occur in patients who have PD (eg, Parkinson's disease [aggravation], dyskinesia, dizziness, tremor) or who are treated with dopaminergic agents (eg, nausea, vomiting, hallucinations) or transdermal systems.
- Generally, there were no differences between the 2 rotigotine and placebo treatment groups in the distribution of heart rate values and the relative changes from Baseline. A small, transient, time-related increase in heart rate of up to 3 bpm was observed in all 3 treatment groups. QTc interval changes from Baseline were similar for rotigotine and placebo groups. Overall, changes in electrocardiogram abnormality findings were similar across the 3 treatment groups. There appears to be a dose-related trend for "Broad QRS intraventricular block;" however, this finding is small and may reflect a larger number of abnormalities present in the placebo group at Baseline that subsequently improved.
- 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.
- At Baseline, 72%-74% of subjects in each treatment group reported not being excessively sleepy. The proportion of subjects who were not excessively sleepy at Baseline but reported being excessively sleepy at the end of treatment was slightly less (8%) in the placebo-treated subjects, compared with the 18.0mg/day rotigotine group (10%) and the 27.0mg/day rotigotine group (14%).

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

Other results:

- Rotigotine-treated subjects in both treatment groups had larger decreases in L-DOPA usage at the end of the Maintenance Phase compared with the L-DOPA usage among placebo-treated subjects.
- Across all treatment groups at the end of the Maintenance Phase, there was a small decrease in the mean number of hours that subjects slept (range: -0.1 to -0.2 hour).
- At the end of treatment, there was a minimal decrease in the severity of Parkinson's disease CGI score across all treatment groups. Among subjects in the 18.0mg/day rotigotine group, the proportion of extremely ill and severely ill subjects changed minimally at the end of treatment; however, fewer subjects were markedly or moderately ill. Similarly, among subjects in the 27.0mg/day rotigotine group, the proportion of extremely ill and markedly ill subjects changed minimally; however, fewer subjects were severely ill or moderately ill.
- There was minimal 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. Mean changes from Baseline to the end of treatment in the health state score were small across the treatment groups, but tended to show small mean decreases in the placebo group versus small mean increases in the 18.0mg/day rotigotine and 27.0mg/day rotigotine groups.

Conclusions:

- Rotigotine shows efficacy for the treatment of advanced-stage Parkinson's disease in subjects titrated to a target dose of 18.0mg/day or 27.0mg/day and who are not well controlled with L-DOPA.
- The positive treatment effect of rotigotine was represented by a decrease in "off" time without an increase in "on" time with troublesome dyskinesia.
- For subjects receiving rotigotine, improvement was maintained compared with subjects receiving placebo over the 6-month Maintenance Phase.
- The secondary endpoints were supportive of the primary efficacy endpoint and showed consistent improvement in both rotigotine groups.
- Rotigotine was generally well-tolerated when titrated up to 27.0mg/day in patients with

Name of company: SCHWARZ BIOSCIENCES	**Individual study table referring to part of the dossier** NA	*(For National Authority Use Only)*
Name of Finished Product:	**Volume:** Not applicable	
Name of Active Ingredient: Rotigotine	**Page:** Not applicable	

advanced-stage Parkinson's disease who were receiving treatment with L-DOPA.

- The dose titration scheme used in the trial was well-tolerated and is, therefore, appropriate for use in patients with advanced-stage Parkinson's disease.
- The adverse events seen are generally similar to those attributed to other dopaminergic agonists.
- Rotigotine is weakly irritating to the skin compared with placebo and showed a dose (patch size)-related increase in application and instillation site reactions that were generally well-tolerated.
- The dose de-escalation scheme used in this trial allows for safe and tolerable withdrawal of the drug from subjects.

Date of the report: 14 Nov 2005