CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	NDA 21-829
Drug Name:	Rotigotine
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Applicant:	Schwarz Pharma
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Keywords: *NDA review, endpoint analysis/LOCF, multi-center*

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1. EXECUTIVE SUMMARY

The sponsor has submitted the efficacy findings of two pivotal phase III trials (SP512-Part 1 & SP513-Part-1) to demonstrate the efficacy of rotigotine in treating the patients with early-stage, idiopathic Parkinson's disease. In addition, the sponsor has also submitted findings of several Phase 2 dose-ranging trials of rotigotine for treating Early-Stage, Idiopathic Parkinson's Disease.

In this review, two pivotal phase III trials (SP512-Part-1 & SP513-Part-1) and one supportive study (SP506) are reviewed. All of the three studies demonstrate statistically significant efficacy of rotigotine in treating the patients with early-stage, idiopathic Parkinson's disease.

1.1. Conclusions and Recommendations

This statistical review confirms the sponsor's claim on the positive efficacy of rotigotine. That is, the findings of the two pivotal phase III trials demonstrate that Rotigotine was effective for the treatment of early-stage PD in patients titrated to a target dose of 13.5mg/day in study SP512-Part-1 and 18.0 mg/day in SP513-Part-1.

The supportive study (Study SP506) demonstrates a dose-response relationship in the improvements was evident from 4.5 to 13.5mg. The magnitude of improvement was similar in the rotigotine 13.5 and 18.0mg groups.

1.2. Brief Overview of Reviewed Clinical Studies

1.2.1. Pivotal Studies

Both pivotal studies SP512 -Part-1 and & SP513-Part-1 were Phase 3, multicenter, multinational, randomized, double-blind, parallel group trial of rotigotine in patients with early-stage, idiopathic Parkinson's disease. The trial periods in both studies consisted of a 4-week pre-treatment (washout) period, a 3-week in SP512-Part-1 and up to 13 weeks in SP513-Part-1 dose escalation period, a 24-week dose maintenance period. Study SP512-Part-1 was conducted in US and Canada, and study SP513-Part-1 was conducted in Europe (including Central and Eastern Europe), Australia/New Zealand, Israel, and South Africa.

In study SP512-Part-1, a total of 181 subjects were randomized to rotigotine and 96 subjects were randomized to placebo. In study SP513-Part-1, a total of 215 subjects were randomized to rotigotine, 228 subjects were randomized to ropinirole, and 118 subjects were randomized to placebo.

In both studies, the primary efficacy variable to measure the efficacy of rotigotine was the change in the UPDRS subtotal score (Parts II+III) from the baseline visit to the end of double-blind maintenance phase.

The primary efficacy measure was analyzed using an analysis of covariance model (ANCOVA) with adjustment terms for geographic region of investigational center and baseline UPDRS (a covariate). The primary analyses were based on the ITT data sets with missing data imputed by Last-Observation-Carried-Forward (LOCF).

1.2.2. Supportive Study

SP506 was a phase IIb, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to compare the efficacy, safety, and tolerability of rotigotine versus placebo in early-stage Parkinson's disease patients during a 12-week period. Patients were randomized to receive 1 of 4 target doses of rotigotine (4.5mg/day, 9.0mg/day, 13.5mg/day, 18.0mg/day or placebo). The study was conducted in 51 sites (36 sites in the US and Canada and 15 sites in Estonia, India, Latvia, Lithuania, Poland, South Africa, and Ukraine).

A total of 329 patients were randomized to rotigotine (67 patients to 4.5mg, 63 patients to 9.0mg, 65 patients to 13.5mg, and 70 patients to 18.0mg) and placebo (64 patients).

The primary outcome variable was efficacy of rotigotine as measured by a change in UPDRS Parts II + III score from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77).

The primary efficacy measure was analyzed using ANCOVA with adjustment terms for country included as a stratification factor and baseline UPDRS (a covariate). The primary analysis of the primary variable was based on the ITT data set with missing data imputed by LOCF.

1.3 Statistical Issues and Findings

No statistical issues were found in the three reviewed studies.

2. INTRODUCTION

2.1. Overview

The sponsor has submitted the efficacy findings of two pivotal phase III trials (SP512-Part-1 & SP513-Part-1) to demonstrate the efficacy of rotigotine in treating the patients with early-stage, idiopathic Parkinson's disease. Table 1 lists an overview of the studies.

Table 1: Overview of the Pivotal Trials in Early-Stage, Idiopathic Parkinson's Disease.

Trial Number/Clinical Development Phase/Trial Design	# Subjects Receiving Rotigotine[a]	# Subjects Receiving Placebo[a]	# Subjects Receiving Active Control	Maintenance Duration
SP512 Part I[b]/Phase 3/MC, DB, PC, parallel-group, efficacy, safety in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, and 13.5mg daily doses.	181	95	NA	6 months
SP513 Part I[b]/Phase 3/MC, DB, placebo- and active-controlled, parallel-group, efficacy, safety in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	215	118	228 (ropinirole)	6 months
Total	396	213	228	–

a These subject exposures are based on the safety analysis dataset.
b Meets the definition of an adequate and well-controlled trial for registration in the US.
DB=double-blind, MC=multicenter, NA=not applicable, PC=placebo-controlled
Source of the table: ISE report .

In addition, the sponsor has also submitted several Phase II dose-ranging trials of rotigotine for treating Early-Stage, Idiopathic Parkinson's Disease.

2.2. Data Sources

SAS data sets of each of the pivotal studies are available at "V:\N021829\0000\m5\53-clin-stud-rep\537-crf-ipl\. The study reports are available at V:\N021829\0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\5351-stud-rep-contr.

3. STATISTICAL EVALUATION

3.1. Study reviewed

In this statistical review, efficacy findings of the two pivotal studies (SP512 Part-1 and SP513-Part-1) are reviewed. In addition, one supportive phase II study (SP506) is also reviewed and the review is provided at the end of efficacy review of the two pivotal studies. The study SP506 was a fixed doses (4.5mg, 9.0mg, 13.5mg, 18.0mg, or placebo) study. The review of this study will help us in determining the target dose. The efficacy findings of other phase II studies are provided in the attachment-1.

3.1.2. Study Design - SP512-Part-1 and SP513-Part-1.

SP512-Part 1 was a Phase 3, multicenter, multinational, randomized, double-blind, placebo controlled, 2-arm, parallel group trial of rotigotine (4.5, 9.0, or 13.5mg/day) in patients with early-stage, idiopathic Parkinson's disease. A total of 181 subjects were randomized to rotigotine and 96 subjects were randomized to placebo. Study 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. The study was conducted in 50 sites located in US and Canada.

In SP512-Part-1, all randomized patients started the titration phase at a daily dose of 4.5mg. Patients were then up-titrated, at 7 day intervals, in 4.5mg increments to a maximum daily dose of 13.5mg. The maximum length of the titration phase was 3 weeks although not all patients required 3 weeks to reach their optimal dose. When a patient completed titration period, the patients remained at that dose and began the 6-month (24-week) maintenance phase.

SP513-Part-I was a Phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo- and ropinirole-controlled, trial of the efficacy of rotigotine in patients with early-stage, idiopathic Parkinson's disease. Rotigotine maintenance doses included 4.5mg/day, 9.0mg/day, 13.5mg/day, and 18.0mg/day; ropinirole maintenance doses ranged from 0.75mg/day to 24.0mg/day. A total of 215 subjects were randomized to rotigotine, 228 subjects were randomized to ropinirole, and 118 subjects were randomized to placebo. The study was conducted in 85 sites located in Europe (including Central and Eastern Europe), Australia/New Zealand, Israel, and South Africa.

In SP513-Part-I, all randomized patients started the titration phase at a daily dosage of 4.5mg rotigotine/placebo and 0.75mg (0.25mg three times a day [tid]) ropinirole/placebo. Patients were then up-titrated, at 7-day intervals to a maximum dose of 18.0mg/day rotigotine/placebo or 24.0mg/day ropinirole/placebo. The maximum length of the titration phase was 13 weeks although not all patients required 13 weeks to reach their optimal dose. When the titration period was completed for a patient, the patient remained at that dose and began the 6-month (24-week) maintenance phase.

3.1.3. Patient Population – Studies SP512-Part-1 and SP513-Part-1.

The patients were outpatients and were from both genders. Patients were included in the studies if they had been diagnosed with idiopathic PD 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; had at least 2 or more of the following cardinal signs: bradykinesia, resting tremor, rigidity, postural instability, and were without any other known or suspected cause of Parkinsonism.

If a patient had been receiving an anticholinergic agent (ie, benztropine, trihexyphenidyl, parsitan, procyclidine, biperiden), an MAO-B inhibitor (ie, selegeline), an N-methyl-Daspartate (NMDA)-antagonist (eg, 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.

Patients were excluded from the trials (i) if they had prior or concurrent therapy with a dopamine agonist within 28 days of the baseline visit; (ii) if they had prior therapy with carbidopa/levodopa within 28 days of baseline; (iii) if they had received carbidopa/levodopa for more than six months since diagnosis; (iv) if the subject had atypical Parkinson's syndrome(s) due to drugs (eg, neuroleptics, metoclopramide, flunarizine), metabolic neurogenetic disorders (eg, Wilson's disease), encephalitis, cerebrovascular disease or degenerative disease (eg, progressive supranuclear palsy); (v) or if the subject had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant.

3.1.4. Efficacy Parameters – Studies SP512-Part-1 and SP513-Part-1.

In both SP512-Part-I and SP513-Part- I studies, the primary efficacy variable to measure the efficacy of rotigotine was the change in the UPDRS subtotal score (Parts II+III) from the baseline visit to the end of double-blind maintenance phase.

The secondary efficacy measures were (i) Percent change in the UPDRS subtotal (Parts II+III) from the baseline visit to the end of the double-blind maintenance phase, (ii) Change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part II, (iii) Change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part III, and (iv) Area under the curve (AUC) for the change from baseline values of the UPDRS subtotal (Parts II+III) during the double-blind maintenance phase.

3.1.5. Statistical Analyses – Studies SP512-Part-1 and SP513-Part-1.

In both SP512-Part-I and SP513-Part-I studies, the primary efficacy measure was analyzed using an analysis of covariance model (ANCOVA) with adjustment terms for geographic region of investigational center and baseline UPDRS (a covariate). The primary analysis of the primary variable was based on the ITT data set with missing data imputed by Last-Observation-Carried-Forward (LOCF). The secondary efficacy measures were also analyzed using ANCOVA models.

3.1.6. Handling Missing Data - Studies SP512-Part-1 and SP513 -Part-1.

Missing UPDRS data at the end of the double-blind maintenance phase due to withdrawal or missing at the planned visit were imputed with the most recent post-baseline observation available for each subject. That is, the "last observation carried forward" principle was Utilized in replacing missing UPDRS efficacy data.

3.1.7. Sponsor's Results – Studies SP512-Part-1 and SP513-Part-1.

3.1.7.1. Patient Characteristics - Studies SP512-Part-1 and Sp513-Part-1.

Within each study, the distributions of patients by gender, age, and race were well balanced across the treatment groups. Majority of patients were male and nearly all patients were white. There were no important differences in baseline characteristics between treatment groups at DB Baseline within each study (Table 2).

Table 2: Demographic Characteristics of the Randomized Patients

	Placebo (N=96)	Rotigotine (N=181)	
Study: SP512-Part-1	N (%)		
Gender : Male	58 (60%)	123 (68%)	
Female	38 (40%)	58 (32%)	
Race: White	92 (96%)	175 (97%)	
Black/Asian/Other	4 (4%)	6 (3%)	
Age: <65 years	43 (45%)	109 (60%)	
65- 74 years	33 (34%)	52 (29%)	
>=75 years	20 (21%)	20 (11%)	
Study: SP513-Part-1			
	Placebo (N=118)	Rotigotine (N=215)	Ropinirole (N=228)
Gender : Male	69 (58%)	119 (55%)	137 (60%)
Female	49 (42%)	96 (45%)	91 (40%)
Race: White	114 (97%)	206 (96%)	218 (96%)
Black/Asian/Other	4 (3%)	9 (4%)	10 (4%)
Age: <65 years	71 (60%)	121 (56%)	136 (60%)
65- 74 years	42 (36%)	85 (40%)	71 (31%)
>=75 years	5 (4%)	9 (4%)	21 (9%)

Source: Study reports of SP512 & SP513

Table 3 lists the patient disposition of the two studies. Within each study, patient discontinuation rates were similar across treatment groups. In both studies, the discontinuation rates were most often due to adverse events and lack of efficacy. The withdrawal rates due to adverse events were higher for Rotigotine group.

Table 3: Summary of Patient Disposition

For Study #SP512-Part-1	Placebo	Rotigotine	
Entered Double-Blind	96	181	
ITT Population	96	181	
Completed Treatment*	81 (84%)	142 (78%)	
Subjects prematurely discontinuing trial	15 (16%)	39 (22%)	
Reasons for prematurely discontinuation**:			
Adverse Event	6 (6%)	25 (14%)	
Lack of efficacy	6 (6%)	12 (7%)	
Subject withdrew consent	4 (4%)	6 (3%)	
Other/Administrative/ Lost to follow-up	2 (2%)	2 (1%)	
For Study # Sp513-Part-1			
	Placebo	Rotigotine	Ropinirole
Entered Double-Blind	118	215	228
ITT Population	117	213	227
Completed Treatment	84 (71%)	151 (70%)	174 (76%)
Withdrawn Prior to End of Treatment	34 (29%)	64 (30%)	54 (24%)
Withdrawn Due to:			
Adverse Event	6 (5%)	37 (17%)	29 (13%)
Lack of efficacy	22 (19%)	14 (7%)	8 (4%)
Subject withdrew consent	7 (6%)	18 (8%)	15 (7%)
Other/Administrative/ Lost to follow-up	6 (5%)	6 (3%)	20 (9%)

Sources: Table# 3.1 & 3.2 in the study reports.
*Completion of trial is defined as having the full 24 weeks of Maintenance Phase medication.
**It was possible to tick more than one reason for termination.

3.1.7.2. Primary Efficacy Analyses- Studies SP512-Part-1 and SP513-Part-1.

Table 4 lists the primary efficacy results of the studies based on the primary efficacy measure-the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III). In both studies, the findings indicate that Rotigotine was statistically significantly (P-values<.0001) superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease. In Study SP513-Part-1, the active control Ropinirole was also significantly (P-value<.0001) superior to placebo.

Table 4: LOCF ANCOVA Results for Change from Baseline to End of Maintenance Phase for UPDRS Subtotal (Part II+III)- ITT Population.

Study/Treatment	Least Squares			
	Mean	SE	Difference from placebo	P-value
Study#SP512-Part-1				
Placebo	1.31	0.956	--	
Rotigotine	-3.98	0.707	-5.28	<0.0001
Study#SP513-Part-1				
Placebo	-2.33	0.882	--	
Rotigotine	-6.83	0.659	-4.49	<0.0001
Ropinirole	-10.78	0.637	-8.45	<0.0001

Source: table 10.1 from the study reports.

Table 5 lists the observed cases (i.e., available cases) analysis on UPDRS subtotal (Part II+ III) at each visit in the maintenance phase. In both trials, at each visit, Rotigotine was statistically significantly (P-value<.001) superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease.

Table 5: Observed Cases ANCOVA Results for Change from Baseline to each Visit in the Maintenance Phase for UPDRS Subtotal (Part II+III)- ITT Population

Study#SP512 (Part 1)						Study#SP513 (Part 1)					
Day/ Treatment Group	N	Least Square Means	SE	Diff. from Placebo	P-value (vs. Placebo)	Day/ Treatment Group	N	Least Square Means	SE	Diff. from Placebo	P-value (vs. Placebo)
Day 29 MP*						Day 29 MP*					
Placebo	87	-3.19	0.747	--	--	Placebo	95	-6.99	0.870	--	--
Rotigotine	166	-6.47	0.542	-3.28	0.0004	Rotigotine	173	-10.67	0.649	-3.67	0.0007
						Ropinirole	186	-13.13	0.624	-6.14	<.0001
Day 57 MP*						Day 57 MP*					
Placebo	85	-2.51	0.841	--	--	Placebo	90	-5.91	0.895	--	--
Rotigotine	155	-6.64	0.625	-4.13	<.0001	Rotigotine	165	-10.28	0.664	-4.37	<.0001
						Ropinirole	179	-13.21	0.635	-7.30	<.0001
Day 85 MP*						Day 85 MP*					
Placebo	84	-1.73	0.867	--	--	Placebo	86	-5.49	0.950	--	--
Rotigotine	152	-5.68	0.649	-3.95	0.0003	Rotigotine	156	-9.83	0.706	-4.34	0.0002
						Ropinirole	176	-13.14	0.662	-7.65	<.0001
Day 113 MP*						Day 113 MP*					
Placebo	82	-0.62	0.884	--	--	Placebo	84	-5.24	1.000	--	--
Rotigotine	145	-5.78	0.673	-5.16	<.0001	Rotigotine	153	-9.27	0.740	-4.03	0.0011
						Ropinirole	175	-13.14	0.689	-7.90	<.0001
Day 141 MP*						Day 141 MP*					
Placebo	80	-0.11	0.898	--	--	Placebo	82	-4.38	1.064	--	--
Rotigotine	141	-5.52	0.683	-5.41	<.0001	Rotigotine	152	-8.57	0.781	-4.20	0.0014
						Ropinirole	174	-12.96	0.727	-8.58	<.0001
End of MP*						End of MP*					
Placebo	81	0.89	1.063	--	--	Placebo	83	-3.17	1.046	--	--
Rotigotine	140	-4.42	0.817	-5.31	<.0001	Rotigotine	151	-7.65	0.774	-4.48	0.0005
						Ropinirole	173	-12.36	0.721	-9.19	<.0001

*MP=Maintenance Period.

Source: Sponsor's submission on June 23, 2005

3.1.7.3. Secondary Efficacy Analyses- Studies SP512-Part-1 and Sp513-Part-1.

Table 6 lists the efficacy results of the secondary efficacy measures (i) Percent change in the UPDRS subtotal (Parts II+III) from the baseline visit to the end of the double-blind maintenance phase, (ii) Change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part II, (iii) Change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part III, and (iv) Area under the curve (AUC) for the change from baseline values of the UPDRS subtotal (Parts II+III) during the double-blind maintenance phase. In both studies, each of the secondary measures demonstrated that Rotigotine was statistically significantly (Pvalue<.0001) superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease.

Table 6: LOCF ANCOVA Results for the Secondary efficacy measures- ITT Population.

Study / Secondary measures	Treatment	Least Squares			
		Mean	SE	Difference from placebo	P-value
Study#SP512-Part-1					
UPDRS Subtotal (Parts II + III): Percent Change from Baseline to end of Maintenance Phase	Placebo	7.25	3.75	--	
	Rotigotine	-15.1	2.77	-22.3	<0.0001
UPDRS Subtotal (Parts II + III): Area Under the Curve (AUC) during Maintenance Phase for the Changes from baseline	Placebo	-157	118.98	--	
	Rotigotine	-941	87.99	-784	<0.0001
UPDRS Part II only (activities of daily living): Change from baseline	Placebo	0.91	0.348	--	
	Rotigotine	-0.38	0.257	-1.29	0.0029
UPDRS Part III only (motor examination): Change from baseline	Placebo	0.40	0.730	--	
	Rotigotine	-3.60	0.540	-4.00	<.0001
Study#SP513-Part-1					
UPDRS Subtotal (Parts II + III): Percent change from Baseline to end of Maintenance Phase	Placebo	-6.00	2.80	--	
	Rotigotine	-23.19	2.09	-17.19	<0.0001
	Ropinirole	-33.93	2.02	-27.93	<0.0001
UPDRS Subtotal (Parts II + III): Area Under the Curve (AUC) during Maintenance Phase for the Changes from baseline	Placebo	-748.81	139.18	--	
	Rotigotine	-1489.07	104.04	-740.25	<0.0001
	Ropinirole	-1975.57	100.66	-1226.76	<0.0001
UPDRS Part II only (activities of daily living): Change from baseline	Placebo	-0.24	0.321	--	
	Rotigotine	-1.91	0.240	-1.68	<.0001
	Ropinirole	-3.02	0.212	-2.78	<.0001
UPDRS Part III only (motor examination): Change from baseline	Placebo	-2.10	0.669	--	
	Rotigotine	-4.92	0.500	2.82	0.0007
	Ropinirole	-7.76	0.483	-5.66	<.0001

Source: Sponsor's submission on June 23, 2005

3.1.7.4. FDA Reviewer's Data Analyses and Comment – Studies SP512-Part-1 and Sp513-Part-1.

This reviewer re-analyzed the data sets of both studies according to the protocol specified statistical analysis plans. The findings for the primary and secondary efficacy measures matched with the findings submitted by the sponsor.

3.2. Review of the Supportive Study SP506

3.2.1. Study Design - Study SP506.

Study SP506 was a phase IIb, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to compare the efficacy, safety, and tolerability of rotigotine transdermal delivery system ("patch") versus placebo in early-stage Parkinson's disease patients during a 12-week period. Patients were randomized to receive 1 of 4 target doses of rotigotine (4.5mg/day, 9.0mg/day, 13.5mg/day, 18.0mg/day or placebo). A total of 329 patients were randomized to rotigotine (67 patients to 4.5mg, 63 patients to 9.0mg, 65 patients to 13.5mg, and 70 patients to 18.0mg) and placebo (64 patients).

The trial consisted of a 28-day (maximum) screening period that included a 4- to 7-day open-label, placebo-run-in period; a 28-day double-blind, dose-titration period (dose titration occurred on a weekly basis); a 49-day dose-maintenance period; and a 7-day dose de-escalation period. Subjects were titrated in $10cm^2$ steps (4.5mg rotigotine or placebo) on a weekly basis to a randomized target dose of 4.5, 9.0, 13.5, or 18.0mg active drug (A) or placebo (P), starting with 4.5mg (or placebo). The titration regimen was designed so that each subject started treatment on his/her target dose during the fourth week of titration; thus, subjects in all treatment groups were maintained at their target dose for 7 weeks. The study was conducted in 51 sites (36 sites in the US and Canada and 15 sites in Estonia, India, Latvia, Lithuania, Poland, South Africa, and Ukraine).

3.2.2. Patient Population – Study SP506

The patients were outpatients and were from both genders and age ≥30 years. Patients were included in the study if they had idiopathic Parkinson's disease; had at least 2 of the following cardinal signs (bradykinesia, resting tremor, rigidity, postural instability) being present, without any other known or suspected cause of Parkinsonism; had Hoehn and Yahr Stage ≤3.0; and had Mini Mental State Examination (MMSE) score ≥24.

If a patient had been receiving selegiline, anticholinergic agents (i.e., benztropine mesylate [Cogentin], artane trihexyphenidyl hydrochloride [Artane], ethoproprazine hydrochloride [Parsidol], procyclidine hydrochloride [Kemadrin], biperiden hydrochloride [Akineton]), or 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.

Patients were excluded from the trials (i) if they had prior or concurrent therapy with a dopamine agonist within 28 days of the baseline visit; (ii) if they had prior therapy with carbidopa/levodopa within 28 days of baseline; (iii) if they had received carbidopa/levodopa for more than six months since diagnosis; (iv) if the subject had atypical Parkinson's syndrome(s) due to drugs (e.g., neuroleptics, metoclopramide, flunarizine), metabolic neurogenetic disorders (e.g., Wilson's disease), encephalitis, cerebrovascular disease or degenerative disease (e.g., progressive supranuclear palsy); (v) or if the subject had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant.

3.2.3. Efficacy Parameters – Study SP506

The primary outcome variable was efficacy of rotigotine as measured by a change in UPDRS Parts II + III score from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77).

The secondary efficacy measures were (i) Changes in UPDRS Part I (mentation, behavior and mood), Part II (ADL), and Part III (motor examination) from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77), and (ii) Percent change from baseline in the sum of the motor and ADL components of the UPDRS for subjects with ≥20% decrease and ≥30% decrease in scores; these subjects were classified as "responders."

3.2.4. Statistical Analysis – Study SP506

The primary efficacy measure was analyzed using an analysis of covariance model (ANCOVA) with adjustment terms for country included as a stratification factor and baseline UPDRS (a covariate). The "country" variable was defined as follows: US, Canada, India, and combined (i.e., Lithuania, Estonia, Latvia, Ukraine, Poland, and South Africa). A closed testing procedure was used in conjunction with the above model. The primary analysis of the primary variable was based on the ITT data set with missing data imputed by Last-Observation-Carried-Forward (LOCF). The secondary efficacy measures were also analyzed using ANCOVA models.

3.2.5. Handling of Missing data - Study SP506

Missing UPDRS data at the end of the double-blind maintenance phase were imputed using LOCF approach.

3.2.6. Sponsor's Results – Study SP506

3.2.6.1. Patient Characteristics - Study SP506

The distributions of patients by gender, age, and race were well balanced across the treatment groups. Majority of patients were males and whites. There were no important differences in baseline characteristics between treatment groups at baseline (Table 7).

Table 7: Demographic Characteristics of the Randomized Patients-ITT population

		Rotigotine			
	Placebo (N=62)	4.5mg (N=65)	9.0mg (N=60)	13.5mg (N=61)	18.0mg (N=68)
Study: SP506	%	%	%	%	%
Gender : Male	44%	71%	72%	62%	59%
Female	56%	29%	28%	38%	41%
Race: White	85%	78%	88%	84%	88%
Black/Asian/Other	15%	22%	12%	16%	12%
Age: <65 years	65%	58%	75%	61%	63%
>=65 years	35%	42%	25%	39%	37%

Source: Study reports of SP506

Table 8 lists the patient disposition of the study. Patient discontinuation rates were similar across treatment groups. The discontinuation rates were most often due to adverse events. The withdrawal rates due to adverse events were higher in rotigotine groups, except the 9.0mg group.

Table 8: Summary of Patient Disposition

Study #SP506	Placebo	Rotigotine			
		4.5mg	9.0mg	13.5mg	18.0mg
Entered Double-Blind	64	67	63	65	70
ITT Population	62	65	60	61	68
Completed Treatment*	54 (87%)	55 (85%)	56 (93%)	55 (90%)	59 (87%)
Subjects prematurely discontinuing trial	8 (13%)	10 (15%)	4 (7%)	6 (10%)	9 (13%)
Reasons for prematurely discontinuation:					
Adverse Event	3 (5%)	6 (9%)	2 (3%)	6 (10%)	6 (9%)
Lack of efficacy	3 (5%)	2 (3%)	-	-	1 (1%)
Subject withdrew consent	-	1 (2%)	1 (2%)	-	2 (3%)
Other/Administrative/ Lost to follow-up	2 (3%)	-	1 (2%)	-	-

Sources: Study reports.

3.2.6.2. Primary Efficacy Analyses- Study SP506

Table 9 lists the primary efficacy results of the studies based on the primary efficacy measure-the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III). At the end of treatment, statistically significant differences for the change from baseline in the UPDRS II + III scores were observed between the rotigotine 9.0mg (effect estimate of -3.123), 13.5mg (-4.909), and 18.0mg (-5.035) dose groups, as compared the change in placebo group. Increasing improvement in UPDRS (i.e., larger negative mean change) was observed with increasing dose from rotigotine 4.5mg through 13.5mg, indicating a dose response up to the rotigotine 13.5mg dose. The magnitude of improvement in the rotigotine 13.5 and 18.0mg groups was similar.

No multiplicity adjustment in p-value was considered. This trial was a dose-ranging study. In this review, this study was reviewed to determine the target optimum dose. Since the magnitude of improvement in the rotigotine 13.5 and 18.0mg groups was similar, the optimum dose might be 13.5mg.

Table 9: LOCF ANCOVA Results for Change from Baseline to End of Maintenance Phase for UPDRS Subtotal (Part II+III)- ITT Population.

Study/Treatment	Least Squares			
	Mean	SE	Difference from placebo	P-value
Study#SP506				
Placebo	-2.52	0.923		
Rotigotine 4.5mg	-4.05	0.924	-1.537	0.212
Rotigotine 9.0mg	-5.46	0.966	-2.940	0.019
Rotigotine 13.5mg	-7.30	0.939	-4.782	0.0002
Rotigotine 18.0mg	-7.33	0.900	-4.817	<0.0001

Source: Calculated by FDA reviewer

Table 10 lists the observed cases (i.e., available cases) analysis on UPDRS subtotal (Part II+ III) at each visit in the maintenance phase. In both trials, at each visit, Rotigotine was statistically significantly (P-value<.001) superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease.

Table 10: Observed Cases ANCOVA Results for Change from Baseline to each Visit in the Maintenance Phase for UPDRS Subtotal (Part II+III)-ITT Population

Visit		Rotigotine			
		4.5mg	9.0mg	13.5mg	18.0mg
Visit 3	LSMean diff. from Placebo	0.644	0.937	-0.546	-1.081
	p-value	0.458	0.290	0.535	0.208
Visit 4	LSMean diff. from Placebo	-0.751	-2.084	-3.542	-2.890
	p-value	0.508	0.069	0.001	0.010
Visit 5	LSMean diff. from Placebo	-1.303	-2.630	-3.108	-3.141
	p-value	0.261	0.024	0.007	0.006
Visit 6	LSMean diff. from Placebo	-1.035	-2.573	-4.116	-4.247
	p-value	0.410	0.046	0.001	<0.001

Source: calculated by FDA reviewer.

3.2.6.3. Secondary Efficacy Analyses- Study SP506.

Table 11 lists the efficacy results of the secondary efficacy measures (i) Changes in UPDRS Part I (mentation, behavior and mood), Part II (ADL), and Part III (motor examination) from baseline visit (Visit 2, Day 0) to Week 11 (Visit 6, Day 77), and (ii) Percent change from baseline in the sum of the motor and ADL components of the UPDRS ($\geq$ 20% decrease and $\geq$ 30% decrease in scores).

UPDRS Part 1 scores (which measure behavioral symptoms) were not changed from baseline in any treatment group at the end of treatment. Improvement in all rotigotine dose groups was numerically greater than improvement in the placebo group with respect to UPDRS Part II scores (activities of daily living (ADL)). The 18.0mg dose demonstrated the greatest improvement compared with the placebo group.

Rotigotine was efficacious in improving motor function as measured by the UPDRS III. At the end of treatment, each of the rotigotine groups had numerically better improvement compared to the placebo group. Increasing improvement in UPDRS (i.e., larger negative mean change) was observed with increasing dose, up through 13.5mg, with similar improvement observed in the rotigotine 13.5 and 18.0mg groups.

The proportions of subjects showing ≥20% and ≥30% decreases in UPDRS scores II+III increased with increasing rotigotine dose. Responder rates were similar in the rotigotine 13.5 and 18.0mg dose groups.

Table 11: LOCF ANCOVA Results for the Secondary efficacy measures- ITT Population.

Measure	**Study SP506**	Placebo	Rotigotine			
			4.5mg	9.0mg	13.5mg	18.0mg
UPDRS Part I	LSMean diff. from Placebo		0.029	0.049	0.013	0.150
	p-value		-	-	-	-
UPDRS Part II	LSMean diff. from Placebo		-0.385	-0.784	-0.647	-1.257
	p-value		-	-	0.631	0.0012
UPDRS Part III	LSMean diff. from Placebo		-1.762	-2.314	-4.296	-3.802
	p-value		0.0401	0.0124	<0.0001	0.0001
Responder Rates at End of Treatment						
		n (%)	n (%)	n (%)	n (%)	n (%)
UPDRS Part II+III	≥ 20% decrease	18 (29%)	25 (38%)	27 (45%)	35 (57%)	36 (53%)
	p-value (vs. Placebo)		0.2418	0.0600	0.0016	0.0057
	≥ 30% decrease	13 (21%)	13 (20%)	16 (27%)	25 (41%)	30 (44%)
	p-value (vs. Placebo)		0.9185	0.4415	0.0176	0.0058

Source: Study report.
ANCOVA Model included treatment group as a factor, country as a stratification factor, and baseline value as a covariate.

3.2.6.4. FDA Reviewer's Data Analyses and Comment – Studies SP506

This reviewer re-analyzed the data set according to the protocol specified statistical analysis plan. The findings for the primary and secondary efficacy measures matched with the findings submitted by the sponsor.

4. Subgroup Analyses

4.1. Subgroup Analyses – Studies SP512-Part-1 and Sp513-Part-1.

In both studies, subgroup analyses on the primary efficacy measure- the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III) were performed to evaluate the uniformity of treatment effect within patient subgroups (gender and age). In both studies, no subgroup analyses were done on race because nearly all patients were white.

Table 12 lists the mean and standard deviation of the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III) by each subgroup. In study SP512-Part-1, the subgroup analyses showed greater efficacy of rotigotine in males, and non-elderly subjects compared with females, and elderly subjects, respectively. In study SP513-Part-1, Subgroup analyses showed no substantial differences in efficacy of rotigotine across the subgroups.

The FDA reviewer also did the subgroup analyses on both studies. The reviewer's conclusions based on the findings were comparable with the sponsor's conclusions.

Table 12: Subgroup Analysis - UPDRS Subtotal (Parts II + III)-ITT Population (With LOCF)

	Change from Baseline to end of Maintenance Phase								
	Placebo			Rotigotine					
Study: SP512-Part-1	n	Mean	SD	n	Mean	SD			
Gender : Male	58	1.3	9.32	121	-4.5	9.17			
Female	38	1.7	8.20	56	-2.4	10.45			
Age: <65 years	43	2.4	9.68	107	-4.8	8.72			
65- 74 years	33	0.4	7.57	52	-2.2	10.55			
>=75 years	20	1.3	9.18	18	-2.2	11.50			
Study: SP513-Part-1	Change from Baseline to end of Maintenance Phase								
	Placebo			Rotigotine			Ropinirole		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Gender : Male	68	-2.5	10.99	118	-8.1	9.89	136	-12.0	11.41
Female	49	-1.9	9.02	95	-6.1	9.84	91	-9.5	8.76
Age: <65 years	70	-1.2	10.18	120	-6.4	9.20	136	-10.3	10.68
65- 74 years	42	-4.4	10.34	84	-8.5	11.01	70	-12.9	10.86
>=75 years	5	1.2	5.93	9	-7.0	7.38	21	-9.6	6.84

Source: Table 12 in the study reports.
Note: In both studies, >96% patients are Whites. So, no subgroup analysis has been done on race.

4.2. Subgroup Analyses – Study SP506

Subgroup analyses on the primary efficacy measure- the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III) were performed to evaluate the uniformity of treatment effect within patient subgroups (gender, age, and US/Canadian vs. Non US/Canadian). No subgroup analyses were done on race because majority of patients were whites.

Table 13 lists the mean and standard deviation of the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III) by each subgroup. Subgroup analyses showed no substantial differences in efficacy of rotigotine across the subgroups.

The FDA reviewer also did the subgroup analyses. The reviewer's conclusions based on the findings were similar with the sponsor's conclusions.

Table 13: Subgroup Analysis - UPDRS Subtotal (Parts II + III)-ITT Population (With LOCF)

Measure	**Study: SP506**		Placebo	Rotigotine			
				4.5mg	9.0mg	13.5mg	18.0mg
UPDRS I+II	Male	n	27	46	43	38	40
		Mean change from baseline	0.11	-4.04	-4.74	-6.61	-7.78
		SD	7.116	7.714	6.691	7.546	8.690
	Female	n	35	19	17	23	28
		Mean change from baseline	-2.54	-2.16	-3.76	-5.65	-4.18
		SD	8.378	5.881	7.259	5.373	5.913
	Age <65	n	40	38	45	37	43
		Mean change from baseline	-1.73	-4.37	-4.91	-6.62	-6.91
		SD	7.545	7.670	6.802	6.930	7.819
	Age≥ 65	n	22	27	15	24	25
		Mean change from baseline	-0.77	-2.26	-3.13	-5.67	-5.24
		SD	8.668	6.508	6.885	6.638	7.881
	US/ Canadian Subjects	n	45	49	45	44	49
		Mean change from baseline	-0.29	-1.71	-3.00	-5.39	-5.22
		SD	7.656	5.948	6.292	6.821	7.069

	Non US/ Canadian Subjects	n	17	16	15	17	19
		Mean change from baseline	-4.29	-8.94	-8.87	-8.47	-9.05
		SD	8.037	8.25	6.578	6.316	9.138

Source: Study reports.
Note: Majority of the patients were Whites. So, no subgroup analysis has been done on race.

5. SUMMARY AND CONCLUSIONS

5.1. Collective Evidence of Efficacy in Studies SP512-Part-1 and SP513-Part-1.

In both pivotal studies, Rotigotine demonstrated statistically significantly effective for the treatment of early-stage PD in patients. In study SP512-Part-1, Rotigotine improved the absolute UPDRS (Parts II+III) subtotal score at the end of treatment (approximately -4 points), whereas the score in placebo-treated subjects indicated deterioration (+1.3 points). Similarly, in study SP513-Part-1, the mean change from baseline in absolute UPDRS (Parts II+III) subtotal score to the end of treatment was -6.83 points (indicating improvement) for rotigotine-treated subjects. Placebo-treated subjects experienced improvements of -2.33 points.

Rotigotine also resulted in a higher proportion of responders at the end of treatment compared with placebo. The proportion of responders for rotigotine at the end of treatment was statistically significantly different from placebo.

5.2. Collective Evidence of Efficacy in Study SP506.

Statistically significant differences in improvement of the UPDRS (part II+III) subtotal scores from baseline to Week 11 were observed between the rotigotine 9.0, 13.5, and 18.0mg groups, as compared to the placebo group. A dose-response relationship in the improvements was evident from 4.5 to 13.5mg. The magnitude of improvement was similar in the rotigotine 13.5 and 18.0mg groups.

5.3. Conclusions and Recommendations

Study SP512-Part-1--Rotigotine was effective for the treatment of early-stage PD in patients titrated to a target dose of 13.5mg/day.

Study SP513-Part-1-- Rotigotine was effective for the treatment of early-stage Parkinson's disease in subjects titrated to an optimal dose of up to 18.0mg/day.

Study SP506-- A dose-response relationship in the improvements was evident from 4.5 to 13.5mg. The magnitude of improvement was similar in the rotigotine 13.5 and 18.0mg groups.

APPENDIX I :

Sponsor's findings on the supportive trials

The sponsor's efficacy findings of each of following supportive studies are copied (Cut and Paste) from the sponsor's documents (Ref: Summary of Clinical Efficacy).

Trial No.	Treatment[a]	Number of Randomized/ Completed Subjects	Endpoint[b]	Results	p-value (CI)	Other results and conclusions
SP534 Part 1	Rotigotine: 9.0mg/day 13.5mg/day Placebo	 5/4 5/3 2/1	UPDRS II+III Change from Baseline at End of Treatment	 1.2 0.2 4.5	NE	• In this small trial with limited numbers of subjects in each dose group, subjects with early-stage Parkinson's disease receiving rotigotine had smaller deteriorations in Parkinson's symptoms measured by the UPDRS compared to those receiving placebo. • Fixed initial doses of rotigotine at 9.0 and 13.5mg/day were associated with dopaminergic side effects, including nausea and vomiting in these early-stage Parkinson's subjects. It was concluded that titration from a well-tolerated dose (4.5mg/day) might allow the early-stage Parkinson's subject to become tolerant to the dopaminergic stimulation of the emetic center and thus minimize associated side effects.

Trial No.	Treatment[a]	Number of Randomized/ Completed Subjects	Endpoint[b]	Results	p-value (CI)	Other results and conclusions
SP534 Part 2	Rotigotine: 18.0mg/day Placebo	 10/10 2/2	UPDRS II+III Change from Baseline at End of Treatment	 -3.7 2.5	Rotigotine-Pla: 0.2621 (-16.95, -5.22)	• In this small trial with limited numbers of subjects in each dose group, subjects with early stage Parkinson's disease receiving rotigotine had larger decreases in UPDRS II+III from baseline to end of treatment compared to those receiving placebo, due primarily to improvements in motor scores. • Initiation of rotigotine therapy at 4.5mg/day with weekly increases of 4.5mg/day minimized dopaminergic side effects while allowing reasonably rapid titration to an optimal dose.
SP540	Rotigotine: 4.5-18.0mg/day	31/25[c]	UPDRS II+III Change from Baseline at End of Treatment	All doses combined: -7.4	All doses combined: <0.0001 (-10.33, -4.43)	• Initiation of rotigotine therapy at 4.5mg/day with weekly increases of 4.5mg/day up to 18.0mg/day was well tolerated.

Trial No.	Treatment[a]	Number of Randomized/ Completed Subjects	Endpoint[b]	Results	p-value (CI)	Other results and conclusions
SP512 Part II[d]	Rotigotine: 4.5mg/day 9.0mg/day 13.5mg/day 18.0mg/day 22.5mg/day 27.0mg/day Total	 6 13 166 23 4 1 213	UPDRS II+III Change from Baseline[e]	At Week 37, (9 months of treatment) subjects receiving a modal dose of ≥13.5mg/day had a mean improvement in UPDRS subtotal (Parts II+III) of 3.1 points.	NE	The following is the overall conclusion for both SP512 and SP513 and pertains to the combined treatment in both Parts I (the double-blind part) and II (the open-label part) of these two trials: • Rotigotine is effective for the long-term (12 to 18 months) treatment of early-stage Parkinson's disease in subjects titrated to a dose of 13.5mg/day or 18.0mg/day. The magnitude of this effect is similar to that in the 6-month, double-blind trials.

Trial No.	Treatment[a]	Number of Randomized/ Completed Subjects	Endpoint[b]	Results	p-value (CI)	Other results and conclusions
SP513 Part II[d]	Rotigotine: 4.5mg/day 9.0mg/day 13.5mg/day 18.0mg/day 22.5mg/day 27.0mg/day Total	 5 34 63 252 14 4 372	UPDRS II+III Change from Baseline[c]	At Week 25 of SP513 Part II (6 months of treatment) subjects receiving a modal dose of ≥18.0mg/day had a mean improvement in UPDRS subtotal (Parts II+III) of 8.3 points while subjects receiving 13.5mg/day had a mean improvement of 11.7 points.	NE	The following is the overall conclusion for both SP512 and SP513 and pertains to the combined treatment in both Parts I (the double-blind part) and II (the open-label part) of these two trials: • Rotigotine is effective for the long-term (12 to 18 months) treatmeht of early-stage Parkinson's disease in subjects titrated to a dose of 13.5mg/day or 18.0mg/day. The magnitude of this effect is similar to that in the 6-month, double-blind trials.

ANCOVA=analysis of covariance; CI=confidence interval; NE=not evaluated.
a For SP512 and 513 part II, this represents the maintenance dose.
b The efficacy endpoints in some of these trials included a total UPDRS Parts I-IV score or UPDRS subtotals other than the UPDRS Parts II+III. For comparison with the primary trials, only the scores for UPDRS Parts II+III are included in this table. Additional detai for the efficacy results of these trials may be found in the respective clinical trial reports, which are included in this submission.
c These are the same subjects.
d This is a non-randomized, open-label trial which is ongoing as of this submission. The cut-off date for the data summarized in this submission is 31 Dec 2003.
e The baseline used for all analyses was the original baseline in Part I (ie, the double-blind part) of this trial.

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