Table 2 UPDRS Part III Motor Subscale

III. MOTOR EXAMINATION

18. Speech
0 = Normal.
1 = Slight loss of expression, diction and/or volume.
2 = Monotone, slurred but understandable; moderately impaired.
3 = Marked impairment, difficult to understand.
4 = Unintelligible.

19. Facial Expression
0 = Normal.
1 = Minimal hypomimia, could be normal "Poker Face".
2 = Slight but definitely abnormal diminution of facial expression
3 = Moderate hypomimia; lips parted some of the time.
4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)
0 = Absent.
1 = Slight and infrequently present.
2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3 = Moderate in amplitude and present most of the time.
4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands
0 = Absent.
1 = Slight; present with action.
2 = Moderate in amplitude, present with action.
3 = Moderate in amplitude with posture holding as well as action.
4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)
0 = Absent.
1 = Slight or detectable only when activated by mirror or other movements.
2 = Mild to moderate.
3 = Marked, but full range of motion easily achieved.
4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succesion.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)
0 = Normal.
1 = Mild slowing and/or reduction in amplitude.
2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straightbacked chair, with arms folded across chest.)
0 = Normal.
1 = Slow; or may need more than one attempt.
2 = Pushes self up from arms of seat.
3 = Tends to fall back and may have to try more than one time, but can get up without help.
4 = Unable to arise without help.

28. Posture
0 = Normal erect.
1 = Not quite erect, slightly stooped posture; could be normal for older person.
2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.
4 = Marked flexion with extreme abnormality of posture.

29. Gait
0 = Normal.
1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.
2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3 = Severe disturbance of gait, requiring assistance.
4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)
0 = Normal.
1 = Retropulsion, but recovers unaided.
2 = Absence of postural response; would fall if not caught by examiner.
3 = Very unstable, tends to lose balance spontaneously.
4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased armswing, small amplitude, and poverty of movement in general.)
0 = None.
1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.
2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3 = Moderate slowness, poverty or small amplitude of movement.
4 = Marked slowness, poverty or small amplitude of movement.

efficacy endpoint. Some of the "other" efficacy endpoints are evaluated as secondary efficacy endpoints.

6.1.3 Study Design

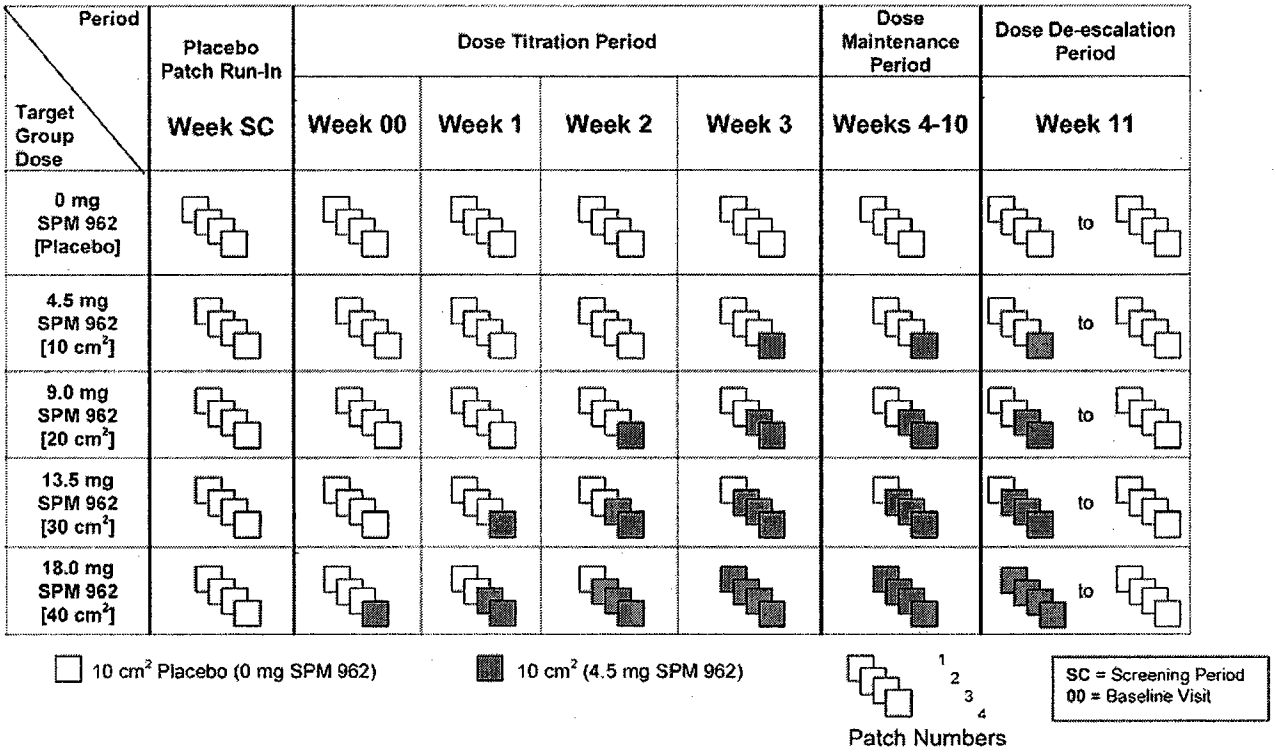
Study 506

Study SP506 was a phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, **fixed dose (dose-finding)** study to compare the efficacy, safety, and tolerability of 4 doses of rotigotine transdermal delivery system ("patch") versus placebo in early-stage Parkinson's disease patients during a period of up to about 12-weeks. 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. 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).

The following schematic diagram illustrates how the titration scheme was achieved for each randomized treatment of placebo and /or rotigotine patch(es).

Proposed Patch Application Scheme: Study SP506 (Part 1)



The patch was applied to the upper abdomen and the site of application was rotated on a daily basis. Patients underwent a weekly titration (increasing the number of patches consisting of 4.5 mg increments at weekly intervals) of placebo or rotigotine patches over 4 weeks such that the randomized, target dose treatment of rotigotine was initiated after 3 weeks and would be administered over the fourth week of the titration phase. Patients then continued on treatment for a 7 week maintenance phase followed by a down titration over the last week. Back/down titration by a single patch (i.e. 4.5 mg decrement of rotigotine or placebo) at a time was permitted for intolerable adverse events. Depending on randomized dose assignment, patients received rotigotine for a total of approximately 8-11 weeks prior to collection of primary efficacy data. Patients were treated with up to four 4.5 mg (10 cm^2) patches of rotigotine and/or placebo. There was a short grace period associated with the planned visits.

Study 512

SP512-Part 1 was a phase 3, multicenter, multinational, randomized, double-blind, placebo controlled, 2-arm, parallel group, **flexible dose** 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. There was a short grace period associated with the planned visits.

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.

Patches were applied to different body parts including upper or lower abdomen (above the umbilicus), thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were supposed to be rotated on a daily basis. Patients underwent a weekly titration (consisting of 4.5 mg increments at weekly intervals) over 3 weeks to a maximal dose of 13.5 mg/24 hours depending on optimal efficacy and tolerability, and then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 4 days. Patients were treated initially with a 4.5 mg (10 cm^2) patch, then a 9 mg (20 cm^2) patch, and finally a 4.5 mg (10 cm^2) and 9 mg (20 cm^2) patch containing rotigotine and/or placebo. Back/down titration by a single patch (i.e. 4.5 mg decrement of Neupro^{TM} or placebo) was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy data were collected after a treatment period of up to approximately 27 weeks of randomized treatment.

Study 513

SP513-Part-I was a Phase 3, multicenter, multinational, randomized, double-blind, double-dummy, placebo- and ropinirole-controlled, trial of the efficacy of **flexible doses** of rotigotine in patients with early-stage, idiopathic Parkinson's disease. This trial also included an active drug comparator (ropinirole) and patients were assigned to treatment with either placebo or rotigotine or active comparator (i.e. ropinirole) in a ratio of 1 : 2 : 2 for a period up to about 39 weeks. 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.

This study was conducted in up to 85 sites in many foreign countries outside of North America. Patches were applied to different body parts including upper or lower abdomen (above the umbilicus), thigh, hip, flank, shoulder, and/ or upper arm and patch application sites were supposed to be rotated on a daily basis. Treatment with a patch and placebo was given to all patients in a double-blinded manner such that no one would know the actual treatment (i.e. Neupro™, ropinirole, or placebo). Patients underwent a weekly dose escalation of patch (consisting of 4.5 mg increments of Neupro™ or placebo) and a dose escalation of capsules of ropinirole or placebo over 13 weeks up to a maximal dose of 18 mg/24 hours of Neupro™ or 24 mg/24 hours (8 mg TID) of ropinirole depending on achieving optimal efficacy or intolerability at a lower dose. Patients randomized to Neupro™ achieved the maximal dose of 18 mg/24 hours if maximal efficacy and intolerability had not occurred over a 4 week titration period. Patients were treated initially with a 4.5 mg (10 cm^2) patch, then a 9 mg (20 cm^2) patch, then a 4.5 mg (10 cm^2) and 9 mg (20 cm^2) patch, and finally two 9 mg (20 cm^2) patches containing rotigotine and/or placebo. Ropinirole or placebo capsules were administered TID, preferably with meals. Patients randomized to ropinirole treatment began at a dose of 0.75 mg daily, and weekly dose escalation occurred at lower increments (0.75 mg) initially and progressively at greater increments (1.5 mg/week and then 3 mg/week) over the 13 week titration phase depending on achieving optimal efficacy or intolerability. Patients then received treatment over a 24 week maintenance phase followed by a de-escalation over a period up to 12 days. A single back/down titration by a single patch (i.e. 4.5 mg decrement of Neupro™ or placebo) or capsule was permitted during the titration phase for intolerable adverse events but was not permitted during the maintenance phase (i.e. patients with intolerable adverse events had to discontinue from this study). Primary efficacy data were collected after a treatment period of up to approximately 37 weeks of randomized treatment. There was a short grace period associated with the planned visits.

Patient Population

Study 506

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/LD

within 28 days of baseline; (iii) if they had received carbidopa/LD 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.

Studies 512 and 513

The patients enrolled were outpatients 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 $\geq$ 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 if they had : 1) prior or concurrent therapy with a dopamine agonist within 28 days of the baseline visit; 20 prior therapy with carbidopa/LD within 28 days of baseline; 3) had received carbidopa/LD for more than six months since diagnosis; 4) 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); or 5) a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant.

Statistical Analysis

Study 506

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.

Missing UPDRS data at the end of the double-blind maintenance phase were imputed using last observation carried forward (LOCF) approach.

Studies 512 and 513

In both 512 and 513 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 secondary efficacy measures were also analyzed using ANCOVA models.

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 (i.e. applying the LOCF principle).

6.1.4 Efficacy Findings

Baseline Patient Characteristics

Study 506

The distributions of patients by gender, age, and race were well balanced across the treatment groups. Majority of patients were males and whites. The mean age of patients was approximately 60 years old (range 34 -83 years; approximately 36 % were ≥ 65 years). Most patients (85 %) were Caucasian. There were no important differences in baseline characteristics between treatment groups at baseline (Table 3).

Table 3 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 506 Report

Study 512

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 Caucasian. There were no noteworthy differences in baseline characteristics between treatment groups at DB Baseline

within each study (Table 4). In Study 512, the mean age of patients was approximately 63 years old (range 32 -86 years; approximately 45 % were ≥ 65 years), approximately two-thirds of all patients were men, and nearly all patients were Caucasian. Whereas approximately 90 % of patients randomized to Neupro™ achieved a maximal daily dose of 13.5 mg, approximately 70 % maintained this maximal dose for most (> 20 weeks) of the maintenance phase of the study. Most enrolled patients (≥ 81 %) completed the full treatment period.

Table 4 Demographic Characteristics of the Randomized Patients

Study: SP512	Placebo (N=96)	Rotigotine (N=181)
	N (%)	
Gender : Male	58 (60%)	123 (68%)
Female	38 (40%)	58 (32%)
Race: Caucasian	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%)

Source: Study 512 Report

Study 513

The baseline characteristics of patients by gender, age, and race were similar across the treatment groups. The majority of patients were male and nearly all patients were Caucasian. There were no noteworthy differences in baseline characteristics between treatment groups (Table 5). In Study 513, the mean age of patients was approximately 61 years old (range 30 -86 years; approximately 41 % were ≥ 65 years), nearly 60 % of all patients were men, and nearly all patients were Caucasian. A clear majority (73 %) of all patients completed the full treatment period.

Table 5 Demographic Characteristics of the Randomized Patients

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: Caucasian	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%)

Patient Disposition

Study 506

Table 6 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, with the exception of the 9 mg group. Most randomized patients (≥ 85 %) completed the full treatment period.

Table 6 Summary of Patient Disposition

		Rotigotine			
Study #SP506	Placebo	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%)	-	-

Source: Study 506 Report

Study 512

Table 7 shows the patient disposition of the two studies. Patient discontinuation was slightly more common in the rotigotine group.. Discontinuation was most frequently related to adverse events in the rotigotine group. The most frequent reasons for discontinuation in the placebo group were adverse event and lack of efficacy. The withdrawal rate due to adverse events was higher for rotigotine group.

Table 7 Summary of Patient Disposition

Study 512	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 premature 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%)

Source: 512 Study Report
*Completion of trial is defined as having the full 24 weeks of Maintenance Phase medication.
**It was possible to assign more than one reason for study termination.

Study 513

Table 8 shows the patient disposition. Patient discontinuation rates were fairly similar across the treatment groups. The discontinuation rates were most frequently related to adverse events (in the rotigotine and ropinirole groups) and lack of efficacy (placebo group). The withdrawal rate due to adverse events was highest for the rotigotine group.

Table 8 Summary of Patient Disposition

Study 513			
	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%)

Source: 513 Study Report

Primary Efficacy Analyses

Overall, I did not have any significant concerns about patients with protocol violations nor that efficacy analysis by including these patients may have unduly influenced efficacy results. Patients who had major and minor protocol violations were included in the ITT statistical analyses for the primary efficacy endpoints in the pivotal trials.

Study 506

Table 9 shows the sponsor's 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). Baseline for UPDRS Subtotal (Part II+III) was similar across the treatment groups. At the end of treatment, statistically significant differences ($p < 0.025$ one-sided) based upon the ANCOVA analyses were observed for the change from baseline in the UPDRS II + III scores for the rotigotine 9.0mg (effect estimate of -3.123), 13.5mg (-4.909), and 18.0mg (-5.035) dose groups, as compared relative to the change in placebo group. In this analysis, the mild effect size of the 4.5 mg dose group was not statistically significant but approached statistical significance ($p < 0.025$ one-sided). Increasing improvement in UPDRS (i.e., larger negative mean change) was observed with increasing dose from rotigotine 4.5mg through 13.5mg, indicating an seemingly monotonic dose response up to the rotigotine 13.5mg dose. The magnitude of improvement (e.g. effect estimate = rotigotine - placebo) in the rotigotine 13.5 and 18.0 mg groups was similar.

Note that in the statistical analysis in Table 9 applied a one- sided p-value in which case a critical alpha of 0.025 would be required to show statistical significance. If one applies a two-sided p-value as is normally done in the Agency, then the critical p-value for statistical significance would be 0.05. One can assess the respective p-value for a 2-sided analysis by doubling the p-value. Of particular relevance here, the 2 sided p-value for this primary statistical analysis for the 4.5 mg dose group would be 0.0786, a value approaching statistical significance but not achieving it.

Table 9 Change from Baseline to End of Maintenance Treatment (EOT) in UPDRS II + III Total Scores by Treatment Group- ITT Population

		Rotigotine			
UPDRS II + III	Placebo (N=62)	4.5mg (N=65)	9.0mg (N=60)	13.5mg (N=61)	18.0mg (N=68)
Baseline (Visit 2) mean (SD)	28.02 (11.114)	28.48 (12.050)	28.52 (11.205)	27.57 (13.462)	27.13 (13.405)
EOT (Visit 6) mean (SD)	26.63 (13.491)	24.98 (11.789)	24.05 (11.528)	21.33 (13.328)	20.84 (11.511)
Mean change from baseline (SD)	-1.39 (7.904)	-3.49 (7.233)	-4.47 (6.808)	-6.25 (6.777)	-6.29 (7.825)
ANCOVA comparison [a]					
Effect estimate		-2.148	-3.123	-4.909	-5.035
p-value		0.0393	0.0063	<0.0001	<0.0001
[95% CI]		[-4.544, 0.248]	[-5.571, -0.675]	[-7.341, -2.477]	[-7.406, -2.665]

a Model included treatment group as a factor, country as a stratification factor, and baseline value as a covariate; a 1-sided p-value was obtained. Each significance test was performed at the 2.5% level.

Source Data: Table 15.1.1.1

Table 10 shows results of the LOCF analysis (ITT population) of the change from baseline to end of maintenance phase for the various treatment and the effect estimate that was conducted by

the statistical reviewer (Dr. Siddiqui). Although these results were not identical to those of the sponsor, they were similar and suggested the same impression of efficacy and similar conclusions as had been made based upon the sponsor's analysis. The p value for the lowest dose (4.5 mg) was somewhat greater than that of the sponsor. Dr. Siddiqui informed me that he was not certain as to the specific reason(s) for this difference but did not consider this difference to be of noteworthy significance and I would agree with this view. He suspected that for some unknown reason his analysis was not conducted identically as the sponsor's analysis. The effect estimates of the other 3 higher dose groups were also slightly smaller than those of the sponsor. I also think that one should be mindful of the fact that this numerical, seemingly small therapeutic difference associated with the 4.5 mg dose group was derived from a relatively small number (N = 65) of patients and seemed to reflect a modest therapeutic benefit of this lowest rotigotine dose studied.

Table 10 LOCF ANCOVA Results for Mean Change from Baseline to End of Maintenance Phase and Effect Estimate (Rotigotine – Placebo) for UPDRS Subtotal (Part II+III)- ITT Population

Study/Treatment	Least Squares			
	Mean	SE	Mean Difference from placebo (Effect Estimate)	P-value (2-sided)
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 Statistical Reviewer

Table 11 shows the analysis of observed cases (i.e., available cases) on UPDRS subtotal (Part II+ III) at each visit in the maintenance phase. Rotigotine was nominally, highly statistically significantly (p-value<.001) and superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease beginning at week 4 for the highest dose groups. Results of completers at the final visit/week 11 (after 7 weeks minimal maintenance treatment for 18 mg group) of full rotigotine treatment (prior to dose tapering) showed a similar, monotonic therapeutic effect as did the LOCF/ITT analysis. However, the effect estimate of all rotigotine doses was slightly smaller than that observed in the primary efficacy analysis of the ITT population based upon the LOCF principle.

Table 11 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 (week 2)	LSMean diff. from Placebo	0.644	0.937	-0.546	-1.081
	p-value	0.458	0.290	0.535	0.208
Visit 4 (week 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 (week 7)	LSMean diff. from Placebo	-1.303	-2.630	-3.108	-3.141
	p-value	0.261	0.024	0.007	0.006
Visit 6 (week 11/final visit on full treatment prior to dose taper)	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 statistical Reviewer.
Nominal p-values are shown without any correction for multiplicity.

Study 512

Mean baseline combined UPDRS (Parts II + III) was similar in both groups (29.9-Neupro™ group, 30.0-placebo). Table 12 shows 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). These results indicate that rotigotine was statistically (p-value < 0.0001) superior to placebo in treating patients with early-stage, idiopathic Parkinson's disease.

Table 12 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 (Effect Estimate)	P-value
Study 512				
Placebo N=96	1.31	0.956	--	
Rotigotine N=177	-3.98	0.707	-5.28	<0.0001

Source: Table 10.1 from 512 Study Report

Table 13 shows the results of observed cases (i.e., available cases) analysis on UPDRS subtotal (Part II+ III) at each visit in the maintenance phase. In both trials, Rotigotine was statistically (p-

value <0.001) superior to placebo in treating patients with early-stage, idiopathic Parkinson's disease.

Table 13 ANCOVA Results of Observed Cases for Change from Baseline to each Visit in the Maintenance Phase for UPDRS Subtotal (Part II+III)- ITT Population

Study#SP512 (Part I)					
Day/ Treatment Group	N	Least Square Means	SE	Diff. from Placebo	P-value (vs. Placebo)
Day 29 MP*					
Placebo	87	-3.19	0.747	--	--
Rotigotine	166	-6.47	0.542	-3.28	0.0004
Day 57 MP*					
Placebo	85	-2.51	0.841	--	--
Rotigotine	155	-6.64	0.625	-4.13	<.0001
Day 85 MP*					
Placebo	84	-1.73	0.867	--	--
Rotigotine	152	-5.68	0.649	-3.95	0.0003
Day 113 MP*					
Placebo	82	-0.62	0.884	--	--
Rotigotine	145	-5.78	0.673	-5.16	<.0001
Day 141 MP*					
Placebo	80	-0.11	0.898	--	--
Rotigotine	141	-5.52	0.683	-5.41	<.0001
End of MP*					
Placebo	81	0.89	1.063	--	--
Rotigotine	140	-4.42	0.817	-5.31	<.0001

*MP=Maintenance Period.
Source: Sponsor's submission on June 23, 2005
Nominal p-values are shown without any correction for multiplicity.

The mean exposure to trial medication was 176 days for placebo-treated subjects and 172 days for rotigotine-treated subjects. Among rotigotine-treated subjects, 163/180 subjects (91%) received 13.5mg/day as their maintenance dose, 11/180 (6%) received 9.0mg/day (9 subjects had back-titrated from 13.5mg/day, and 6/180 (3%) received 4.5mg/day

(2 subjects had back-titrated from 9.0mg/day. Among subjects who were maintained on 4.5mg/day, 50% (3/6) of subjects received this dose for at least 20 weeks; 54% (6/11) of subjects who were maintained on 9.0mg/day received this dose for at least 20 weeks; and 71% (115/163) of subjects who were maintained on 13.5mg/day received this dose for at least 20 weeks. Thus, most of the rotigotine treatment occurred at the highest dose (13.5 mg/d) used in this study. In the placebo treatment group, 92/96 subjects (96%) received the 30 cm^2/day patch (the placebo equivalent of 13.5mg/day) as their maintenance dose, 4/96 (4%) received the 20cm^2/day patch (the placebo equivalent of 9.0mg/day; 1 subject had back-titrated down from 30cm^2/day) as their maintenance dose, and no subject received the 10cm^2/day patch (the placebo equivalent of 4.5mg/day) as their maintenance dose.

Study 513

Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2-Neupro™, 31.3-placebo, 32.2-ropinirole). Table 14 shows the primary efficacy results for the primary efficacy measure-the change from baseline to the end of Maintenance Phase for UPDRS Subtotal (Part II+III). These results indicate that rotigotine was statistically (p-value < 0.0001) superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease. The active control ropinirole was also statistically (p-value < 0.0001) superior to placebo.

Table 14 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 (Effect Estimate)	P-value
Study 513				
Placebo N=117	-2.33	0.882	--	
Rotigotine N=213	-6.83	0.659	-4.49	<0.0001
Ropinirole N=227	-10.78	0.637	-8.45	<0.0001

Source: Table 10.1 from 513 Study Report.

Table 15 shows the results of the observed cases (i.e., available cases) analysis on UPDRS subtotal (Part II+ III) at each visit in the maintenance phase. Rotigotine was statistically (p-value < 0.001) superior to placebo in treating patients with early-stage, idiopathic Parkinson's disease.

Table 15 Observed Cases ANCOVA Results for Change from Baseline to each Visit in the Maintenance Phase for UPDRS Subtotal (Part II+III)- ITT Population

Study#SP513 (Part 1)					
Day/ Treatment Group	N	Least Square Means	SE	Diff. from Placebo	P-value (vs. Placebo)
Day 29 MP*					
Placebo	95	-6.99	0.870	--	--
Rotigotine	173	-10.67	0.649	-3.67	0.0007
Ropinirole	186	-13.13	0.624	-6.14	<.0001
Day 57 MP*					
Placebo	90	-5.91	0.895	--	--
Rotigotine	165	-10.28	0.664	-4.37	<.0001
Ropinirole	179	-13.21	0.635	-7.30	<.0001
Day 85 MP*					
Placebo	86	-5.49	0.950	--	--
Rotigotine	156	-9.83	0.706	-4.34	0.0002
Ropinirole	176	-13.14	0.662	-7.65	<.0001
Day 113 MP*					
Placebo	84	-5.24	1.000	--	--
Rotigotine	153	-9.27	0.740	-4.03	0.0011
Ropinirole	175	-13.14	0.689	-7.90	<.0001
Day 141 MP*					
Placebo	82	-4.38	1.064	--	--
Rotigotine	152	-8.57	0.781	-4.20	0.0014
Ropinirole	174	-12.96	0.727	-8.58	<.0001
End of MP*					
Placebo	83	-3.17	1.046	--	--
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
Nominal p-values are shown without any correction for multiplicity.

The majority (198/215) of rotigotine-treated subjects received the maximum dose of 18.0mg/day. The mean dose of rotigotine in the maintenance phase was 17.4 mg/day. Approximately 90 % of patients achieved the maximal daily dose of 18 mg. Twenty-six percent (26%, 60/228) of ropinirole-treated subjects received the maximal dose of 24.0mg/day . The mean dose of ropinirole in the maintenance phase was 14.1mg/day. Among those subjects who did not receive the highest ropinirole dose allowed, no preferred single dose was observed. Fifty-two percent (52%, 61/118) of the placebo-treated subjects completed the full 13 weeks of titration and received the equivalent of 24.0mg/day ropinirole.

Of interest, the sponsor concluded that : "Rotigotine was not non-inferior to ropinirole for the doses tested in this trial design." I would interpret the meaning of this statement to suggest that ropinirole was superior to rotigotine.

Secondary Efficacy Analyses

Unless otherwise noted, all efficacy analyses of secondary efficacy endpoints were conducted without regarding to making adjustments for multiplicity and thus are nominal p values.

Study 506

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Table 16 shows the efficacy results of the secondary efficacy measures : 1) 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 2) 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 $\geq$ 20% and $\geq$ 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 16 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 506 Report
ANCOVA Model included treatment group as a factor, country as a stratification factor, and baseline value as a covariate

Study 512

Table 17 shows the efficacy results for the secondary efficacy measures : 1) percent change in the UPDRS subtotal (Parts II+III) from the baseline visit to the end of the double-blind maintenance phase; 2) change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part II; 3) change from the baseline visit to the end of the double-blind maintenance phase in UPDRS Part III; and 4) area under the curve (AUC) for the change from

baseline values of the UPDRS subtotal (Parts II+III) during the double-blind maintenance phase. Analysis of the secondary measures demonstrated that rotigotine was statistically (p value <0.0001) superior to placebo in treating the patients with early-stage, idiopathic Parkinson's disease.

Table 17 LOCF ANCOVA Results for the Secondary efficacy measures- ITT Population

Study 512 Secondary Efficacy Measures	Treatment	Least Squares			
		Mean	SE	Difference from placebo	P-value
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

Source: Sponsor's submission on June 23, 2005

Study 513

Table 18 shows the efficacy results for the same secondary efficacy measures assessed in study 512. Each of the secondary efficacy measures demonstrated that rotigotine was statistically (p value <0.0001) superior to placebo in treating patients with early-stage, idiopathic Parkinson's disease.

Table 18 LOCF ANCOVA Results for the Secondary efficacy measures- ITT Population

Study 513 Secondary Efficacy Measures	Treatment	Least Squares			
		Mean	SE	Difference from placebo	P-value
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

Subgroup Analyses (Age, Gender, Race, Geographic Study Region)

Study 506

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 19 shows 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 19 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 years	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 years	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

Source: Study 506 Report

Rotigotine was efficacious in treating the manifestations of Parkinson's disease as measured by UPDRS II + III scores in both geographic regions. At the end of treatment in both geographic regions, each of the rotigotine groups had numerically better improvement compared to the placebo group. The results among US/Canadian subjects were similar to those of the overall trial population; subjects from the US/Canadian population comprised approximately three quarters of the total population. Among US/Canadian subjects, increasing improvement in UPDRS II + III scores was observed with increasing dose up through 13.5mg, with similar improvement in the rotigotine 13.5 and 18.0mg groups (Table 20).

Non-US/non-Canadian subjects had higher mean scores at baseline, indicating more severe

disease than US/Canadian subjects (Table 20). Among non-US/non-Canadian subjects, a pronounced placebo response was observed, as well as pronounced responses to rotigotine. Improvements in UPDRS II + III scores were similar across the rotigotine dose groups. Across treatment groups, improvements among non-US/non-Canadian subjects exceeded those among US/Canadian subjects. While there were regional differences in baseline severity and the magnitude of improvement, the results in non-US/non-Canadian subjects followed a similar pattern to those in US/Canadian subjects, with numerically better improvement in each rotigotine group compared with the placebo group. However, the effect estimate in the non- US/non-Canadian subjects did not suggest any dose-response because the treatment effect for all doses was similar. Of further interest, the magnitude of the treatment effect (~ - 9) in these patients was numerically greater than the treatment effect (~ -5) observed in the US/Canadian patients in the two highest dose groups. It is also important to recognize that the number of non-US/non-Canadian subjects was limited, thus caution should be used in the interpretation of treatment group differences based on geographic region.

Table 20 Change from Baseline to End of Treatment (EOT) in UPDRS II + III Total Scores US/Canadian Sites and Non-US/Non-Canadian Sites-ITT Population

UPDRS II + III	Placebo	Rotigotine			
		4.5mg	9.0mg	13.5mg	18.0mg
US/Canadian Subjects					
Number of subjects	N=45	N=49	N=45	N=44	N=49
Baseline (Visit 2) mean (SD)	26.69 (10.804)	26.69 (10.568)	27.51 (10.056)	26.73 (13.651)	23.88 (10.791)
EOT (Visit 6) mean (SD)	26.40 (13.339)	24.98 (10.902)	24.51 (11.681)	21.34 (13.898)	18.65 (10.921)
Mean change from baseline (SD)	-0.29 (7.656)	-1.71 (5.948)	-3.00 (6.292)	-5.39 (6.821)	-5.22 (7.069)
Non-US/non-Canadian Subjects					
Number of subjects	N=17	N=16	N=15	N=17	N=19
Baseline (Visit 2) mean (SD)	31.53 (11.484)	33.94 (14.830)	31.53 (14.081)	29.76 (13.103)	35.53 (15.973)
EOT (Visit 6) mean (SD)	27.24 (14.285)	25.00 (14.583)	22.67 (11.337)	21.29 (12.123)	26.47 (11.340)
Mean change from baseline (SD)	-4.29 (8.037)	-8.94 (8.250)	-8.87 (6.578)	-8.47 (6.316)	-9.05 (9.138)

Source Data: Table 15.1.2.1

506 Study Report

Study 512

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). No subgroup analysis was performed for race because nearly all patients were Caucasian.

Table 21 shows 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. The subgroup analyses showed greater efficacy of rotigotine in males, and in non-elderly patients compared with results in females, and in elderly patients, respectively.

The FDA statistical reviewer also did the subgroup analyses on both studies (512 and 513) based upon the sponsor's 3 categories (< 65 years, 65-74 years, ≥ 75 years). Because the typical consideration of elderly/geriatric patients uses categorical cut-offs of < 65 years vs ≥ 65 years, I asked the sponsor to conduct additional age group analyses based upon the 2 groups. This reviewer's conclusions were fairly similar to the sponsor's original analyses of the 3 age groups and the sponsor's conclusions, namely that rotigotine treatment was associated with greater efficacy in non-elderly patients compared to elderly patients.

Table 21 Subgroup Analysis - UPDRS Subtotal (Parts II + III)-ITT Population (With LOCF)

Study: SP512-Part-1	Change from Baseline to end of Maintenance Phase					
	Placebo			Rotigotine		
	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 years	53	0.8	8.14	70	-2.2	10.71

Source: Table 12 in 513 Study Report for gender and Table 1.2 in sponsor's supplemental analysis for reviewer's request.

Study 513

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). No subgroup analysis was performed for race because nearly all patients were Caucasian.

In study SP513, subgroup analyses for age and gender showed no substantial nor clear differences in efficacy of rotigotine across the subgroups (Table 22). The requested additional analysis of elderly/geriatric patients based upon a 65 year old age cut-off into 2 subgroups did not suggest any different results or conclusions than the analysis of the 3 age groups including a further breakdown of patients who were ≥ 65 years old. There was no suggestion of a substantial different in the treatment effect of rotigotine related to gender or age.

Table 22 Subgroup Analysis - UPDRS Subtotal (Parts II + III)-ITT Population (With LOCF)

Study: SP513	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 years	47	-3.8	10.07	93	- 8.3	10.69	91	-12.2	10.13

Source: Table 12 in 513 Study Report for gender and Table 1.2 in sponsor's supplemental analysis for reviewer's request.

6.1.5 Clinical Microbiology : Not Applicable

6.1.6 Efficacy Conclusions

- Rotigotine is effective as monotherapy of patients with early Parkinson's Disease based upon the primary efficacy analyses of studies SP 506 (fixed dose study), 512 (flexible dose study), and 513 (flexible dose study),.

- A clear rotigotine dose response exists with therapeutic benefit possibly beginning at a daily dose of 4.5 mg and a maximal therapeutic benefit clearly occurs at a daily dose of 13.5 mg. This conclusion is based upon results of study SP506 in which patients were randomized to placebo or one of several fixed doses of rotigotine (i.e. 4.5, 9, 13.5, or 18 mg).

  Considering the suggestion (although not clearly shown statistically for the 4.5 mg dose) of possible efficacy for a population of patients randomized to the daily 4.5 mg dose, the clear indication that efficacy appears to be maximal for a population at daily13.5 mg dose, and that some adverse events increase with dose, especially the highest dose group (daily 18 mg), I think that the recommendation for dosing patients with daily rotigotine should range between 4.5 mg and 13.5 mg. Patients can initiate treatment with 4.5 mg and titrate daily dose increments of 4.5 mg at intervals of at least ≥ 7 days until optimal efficacy or intolerability is achieved.

In interpreting the dose-response data, I think that it important to recognize that the treatment effect of lowest dose (4.5 mg) was based upon a relatively small number of patients and that the 506 study was not powered to show a therapeutic benefit at this lowest dose.

- Of interest, the therapeutic benefit of the active comparator (ropinirole) in the flexible dose titration Study 513 was nearly twice that of rotigotine for the primary efficacy endpoints. Of further interest, ~ 90 % of rotigotine patients were treated at the maximal dose of 18 mg/d and only ~ 26 % of ropinirole patients were treated at the maximal dose 24 mg/d. The average dose of rotigotine was ~ 17 mg/d in the maintenance phase and the average dose of ropinirole was ~ 14 mg/d in the maintenance phase. These results suggest that rotigotine when studied in such a randomized, double-blinded, placebo-controlled, flexible dose/titration study may not be as effective as ropinirole in the treatment of patients with early Parkinson's Disease. Not only when one compares "optimal" doses of rotigotine and ropinirole does rotigotine seem less potent, but particularly when one considers that the average maintenance dose of rotigotine was near the maximal dose but that the average maintenance dose of ropinirole was slightly above half (14 mg/d) of the maximal dose (24 mg/d). Nevertheless, I think that it is important the one be mindful of the fact that the best way to make a head to head to comparison of the effectiveness of rotigotine vs ropinirole would most by comparing both drugs in a study in which patients were randomized (using a double –dummy study design and double-blinded titration up to 23 weeks) to one of several fixed dose of each drug (including low doses to the maximal dose) along with placebo. In such a study, dose-response curves for efficacy of each drug could be constructed and these dose-response curves could be compared to assess the direct comparison of efficacy of each drug.

  Of interest, the sponsor concluded that : "Rotigotine was not non-inferior to ropinirole for the doses tested in this trial design." I would interpret the meaning of this statement to suggest that ropinirole was superior to rotigotine.

7 INTEGRATED REVIEW OF SAFETY

The Integrated Review of Safety was conducted by the Safety Group in the DNP. The Safety Review of this application by Drs. Gerald Boehm, Marc Stone, and Alice Hughes should be sought to obtain information about the safety of rotigotine. In addition, the memo by Dr. Judy Racoosin, Team Leader for the DNP Safety group, addresses and comments on the safety review by Drs. Boehm, Stone, and Hughes.

I have abstracted the Executive Summary of the safety team review and have shown it in section 1.3.3 (Summary of Clinical Findings : Safety).

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor had proposed dosing patients with patches ranging from rotigotine patch content 9-[redacted]mg/day. I think that patients should titrate rotigotine to optimal efficacy and tolerability using doses ranging between 4.5 - 13.5 mg/day. I have noted my specific thoughts about dosing in section 9.4 (Labeling Review).

8.2 Drug-Drug Interactions

Issues related to drug-drug interactions are reviewed by Dr. Ron Kavanagh, Clinical Pharmacology/Biopharmaceutical reviewer.

8.3 Special Populations

Issues related to special populations are addressed ed by Dr. Ron Kavanagh, Clinical Pharmacology/Biopharmaceutical reviewer and the Safety Team review.

8.4 Pediatrics

This drug is not indicated for the intended use of this NDA because Parkinson's Disease does not occur in pediatric patients. [redacted]

8.5 Advisory Committee Meeting

There are no plans at this time that suggest nor stimulate a need for review of this NDA by an Advisory Committee Meeting.

8.6 Literature Review

There are no particular comments relevant to the literature.

8.7 Postmarketing Risk Management Plan

I do not have any particular comments related to a post-marketing risk management plan. One should refer to the safety team review.

8.8 Other Relevant Materials

There are no applicable comments for this section.

9 OVERALL ASSESSMENT

9.1 Conclusions

Rotigotine is effective in the treatment of early Parkinson's Disease.

Rotigotine should be titrated to optimal efficacy and tolerability using doses ranging between 4.5 and 13.5 mg daily.

9.2 Recommendation on Regulatory Action

My recommendation related to a regulator action is that there are no concerns about the efficacy of rotigotine in the treatment early Parkinson's Disease as monotherapy. The efficacy of rotigotine for this indication has clearly been demonstrated.

9.3 Recommendation on Postmarketing Actions

I do not have any particular comments related to a post-marketing risk management plan. One should refer to the safety team review.

9.3.1 Risk Management Activity

I am not aware of any specific program for risk management activity proposed at this time by the safety team with the exception of comments specified in the Executive Summary of the safety team review (section 1.3.3).

9.3.2 Required Phase 4 Commitments

Reference should be made to other reviews.

9.3.3 Other Phase 4 Requests

Reference should be made to other reviews.

I do not have any recommendations for phase 4 request with regard to efficacy issues.

9.4 Labeling Review

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11 Page(s) Withheld

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✓ Draft Labeling

_____ Deliberative Process

9.5 Comments to Applicant

I do not have any comments for the sponsor with regard to efficacy issues.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

Not applicable. See section 9.4 for my labeling review of the section for Clinical Studies and Dosage and Administration.

I do not have any comments for the sponsor with regard to efficacy issues

APPEARS THIS WAY
ON ORIGINAL

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/s/

Leonard Kapcala
2/28/2006 05:13:44 PM
MEDICAL OFFICER

John, Here is my clinical review of efficacy for rotigotine. Please review and sign and let me know if any questions. Thanx. Len

John Feeney
3/6/2006 01:29:01 PM
MEDICAL OFFICER
See my cover memo

MEMORANDUM

NDA 21-829 NEUPRO (rotigotine transdermal system)

INDICATION: Treatment of the Signs and Symptoms of Early Parkinson's Disease

DATE: February 17, 2006

FROM: John Feeney, M.D.
Neurology Team Leader

Rotigotine is a dopamine agonist that has been developed as a transdermal patch for early Parkinson's Disease. It has not been marketed in any other country to date. There are currently 4 dopamine agonists (DAs) available in the US for the treatment of PD: bromocriptine, pergolide, ropinirole, and pramipexole. Bromocriptine and pergolide have both been marketed for many years and are both ergot alkaloids. Ropinirole and pramipexole were approved in the late 1990s and are not ergot derivatives. Rotigotine is also a non-ergot. Ergots are generally believed to carry a risk of fibrotic complications, to include retroperitoneal fibrosis, pleuropulmonary fibrosis, pericardial fibrosis, and valvulopathy. Labeling for the non-ergot dopamine agonists suggests that the risk of fibrotic complications might be less with these drugs.

Rotigotine will be delivered through a transdermal system that will allow for once-daily dosing. Currently, all the oral dopamine agonists available in the US require dosing at least 2- 3 times per day. Therefore, rotigotine will be more convenient to use for some patients and will provide continuous exposure to the drug.

Another dopamine agonist not mentioned in the above discussion is Apokyn (apomorphine), approved in recent years. Apokyn is provided as a dosing pen for intermittent subcutaneous injection for the treatment of "OFF" events in late-stage PD. OFF events occur either unpredictably or as end-of-dose events and are characterized by extreme periods of motor rigidity.

The NDAs for ropinirole and pramipexole were filed with evidence to support their use in both early and advanced PD, as monotherapy and adjunctive therapy with levodopa. In previous meetings between this sponsor and the division, it was agreed that an NDA for rotigotine could be filed specifically for the treatment of early PD. As such, this NDA only includes the results of efficacy studies which enrolled early PD patients not taking levodopa. Studies of the rotigotine patch as adjunctive therapy with levodopa in more advanced PD patients are currently ongoing.

It is generally agreed that levodopa provides greater symptomatic benefits to patients with PD, so while newly diagnosed PD patients might be successfully managed with a dopamine agonist for several years, it is expected that all patients will eventually progress and require levodopa. At this point in time, the efficacy of rotigotine as an adjunct to

levodopa has not been demonstrated, and any approved labeling would have to reflect this fact.

Efficacy

Dr.Leonard Kapcala performed the clinical review of the submitted efficacy data and Dr.Ohidul Siddiqui performed the statistical review. Both have concluded that the sponsor has provided evidence to support the approval of rotigotine for the treatment of early PD.

The sponsor has provided the results of 3 efficacy studies: 506, 512, and 513.

Study 506 was a randomized, placebo-controlled, multiple fixed-dose study. Patients were randomized to: placebo, 4.5mg, 9mg, 13.5mg, or 18mg. A total of 329 patients were randomized and followed for 11 weeks. The primary outcome was change from baseline in UPDRS, parts II and III combined.

The results, as calculated by Dr.Siddiqui, are shown below. Note that no adjustment for multiple dose comparisons was planned in the protocol.

	UPDRS, diff. from placebo	p-value
Placebo	-	-
4.5mg	-1.5	0.212
9mg	-2.9	0.019
13.5mg	-4.8	0.0002
18mg	-4.8	<0.0001

A dose of 4.5mg was not significantly different from placebo. There was no difference between a dose of 13.5mg and 18mg.

Studies 512 and 513 were similar in design. The first was conducted in North America while the other was conducted in Europe, Australia, Israel, and South Africa. In both studies, patients were randomized and treated for 6 months (maintenance phase, after dose escalation). The primary outcome was change from baseline in UPDRS, parts II and III combined. In Study 512, patients were randomized to either placebo or rotigotine. The target dose of rotigotine was 13.5mg. In Study 513, patients were randomized to placebo, rotigotine, or ropinirole. The target dose of rotigotine was 18mg. The target dose of ropinirole was 24mg/day.

In Study 512, 181 patients were randomized to rotigotine and 96 were randomized to placebo. The results are shown below.

	UPDRS, diff. from placebo	p-value
Placebo	-	-
Rotigotine	-5.3	<0.0001

In Study 513, 215 patients were randomized to rotigotine, 228 were randomized to ropinirole, and 118 were randomized to placebo. The results are shown below.

	UPDRS, diff. from placebo	p-value (drug vs. placebo)
Placebo	-	-
Rotigotine	-4.5	<0.0001
Ropinirole	-8.5	<0.0001

In both studies, the difference between rotigotine and placebo was about 5, a difference similar to the one seen in study 506. Note that in Study 513, the difference between rotigotine and ropinirole was 4 in favor of ropinirole.

Inspections

Five domestic inspections were conducted at 2 clinical sites from Study 506 and 3 clinical sites from Study 512. With a few minor exceptions, the data from all sites were deemed acceptable to support a decision for the NDA.

Pharmacology/Toxicology

The usual battery of nonclinical studies was conducted. Dr.Paul Roney performed the pharm/tox review.

Of particular note to Dr.Roney was the general absence of findings in the reproductive toxicology study.

Also surprising to Dr.Roney was the absence of retinal toxicity in the 2-year carcinogenicity studies. The 2 most recently approved dopamine agonists, ropinirole and pramipexole, both were associated with retinal findings in longterm animal studies, suggesting the possibility of a class effect of dopamine agonists.

In the hERG channel assay, the results suggest that rotigotine has the potential to cause QT prolongation with an IC50 of about 150nM.

The in vivo micronucleus study will need to be repeated, perhaps as a Phase 4 commitment. The study was done with IV dosing, an inappropriate route for a chronically administered drug.

The metabolism is characterized adequately for Dr.Roney to conclude that the results of the nonclinical studies are relevant for humans. In both animals and humans, rotigotine is extensively metabolized.

Clinical Pharmacology

This section of the NDA was reviewed by Dr.Ron Kavanagh.

Dr.Kavanagh describes multiple possible metabolic pathways for rotigotine, including glucuronidation, sulfation, N-dealkylation, and oxidation to form a catechol. In vitro studies suggest a role for CYP1A2, 2C19, and 3A4.

Rotigotine showed little propensity to inhibit or induce CYP450 enzymes at clinically relevant concentrations.

Radiolabeled studies have shown that 70% of the absorbed dose is recovered in urine and 20% of the absorbed dose is recovered in feces. After IV administration, the predominant circulating species appear to be the sulfate conjugate, despropyl sulfate, and free rotigotine. Exposures (measured by AUC) are roughly 3-fold higher with the sulfate and 20% higher with the despropyl sulfate, both compared to the free rotigotine.

Safety

The safety review was performed by Drs.Gerard Boehm, Marc Stone, and Alice Hughes, all of the division's Safety Team. Dr.Judy Racoosin, the Safety Team Leader, wrote a cover memo.

The safety database includes subjects from phase 1 studies, trials in early PD, trials in advanced PD, and trials in restless legs syndrome (RLS). The NDA included data through December 2003. The Safety Update (SU) included data through July 2004. Almost all the experience was accrued using the to-be-marketed patch, but some experience is included with 2 earlier versions of the patch.

With the SU, there were 1093 patients with early PD exposed, 575 for more than 6 months and 485 for more than 12 months. There were 128 exposed for more than 2 years. Additionally, there were almost 600 patients with advanced PD exposed and 400 with RLS exposed.

Roughly 300 patients with early PD were exposed to a mean dose of rotigotine of 13.5-18mg/day for 6 months or longer.

There were 2 deaths in early PD trials with rotigotine, both in open-label extension studies. There were also 2 deaths in early PD trials with ropinirole, both during the double-blind phase. The 2 deaths on rotigotine were sudden deaths in relatively young patients, ages 50 and 57 years. One was witnessed and one was unwitnessed.

In advanced PD controlled trials, there were 2 deaths in rotiogotine-treated patients and 2 deaths in placebo-treated patients. In open-label, there were 3 additional deaths in rotigotine treated patients.

No deaths have occurred in RLS trials.

It is possible that all of these fatal events represent background events in this generally older population.

In her cover memo, the Safety Team Leader, Dr.Judy Racoosin, raises concerns about the sudden deaths in conjunction with the occurrence of cardiac arrhythmias in the safety database. For all cardiac rhythm serious AEs and discontinuations due to AEs, she would request a more comprehensive review of the coding and occurrence of such events across all indications. Currently, the safety review is divided according to the specific indications (early PD, advanced PD, RLS, etc.).

There were a number of serious AEs of ventricular arrhythmia noted in the primary safety review. A patient in an open-label extension of Study 513 developed a ventricular arrhythmia, not otherwise specified, that was treated with magnesium and resolved. An 87 y.o. man in the extension of Study 512 fainted and had a positive EP study for inducible ventricular tachycardia. Further, a patient in Study 512 was discontinued with a serious AE of prolonged QT; the subject had a pacemaker placed for a QTc of 545 msec. Another serious AE of prolonged QT interval appears to have been a measuring error.

Several patients also discontinued due to non-serious AEs of prolonged QT and a few others discontinued for non-serious ventricular rhythm problems. One of these, a 64 y.o. man in an RLS study, began having ventricular extrasystoles 3-4 days after starting the patch. Another had a 6 beat run of v.tach. All of these events could possibly represent background events in the population being studied.

Also concerning were the results of 3 early IV studies of rotigotine. In these studies, 29 patients were administered continuous IV infusions of rotigotine, up to 4 hours in two of the studies and up to 7 days in the third study. In the first study (803), 3 patients discontinued because of ventricular ectopy after IV administration. For 2 of these patients, there did appear to be a significant increase in ventricular ectopy related to rotigotine; the results for the other patient are less than convincing. In the third IV study (805), one patient discontinued after 1 day of a planned 7 day infusion because of ventricular tachycardia. For this patient, ventricular ectopy seemed to increase in frequency with increasing dose and duration until ventricular tachycardia occurred. The plasma concentrations at the time of this event were about 1ng/mL, a concentration that will be experienced after administration of the patch.

Common Adverse Events

The profile of common events described in the safety review is consistent with other dopamine agonists approved for PD, with the addition of application site irritation, which was usually mild in intensity.

Adverse Events of Special Interest
A. Sleep Attacks

The labeling for the dopamine agonists includes a class warning about the sudden onset of sleep during activities of daily living. The development program for rotigotine is the first to include targeted monitoring for such events. In controlled trials in early PD, the incidence was 0% for placebo and 1.4% for rotigotine. There were 7 such events reported as serious AEs. At least in one of these, there was no evidence of excessive daytime somnolence (EDS) as measured by the Epworth Sleepiness Scale, prior to the event. For most, the antecedent history for possible EDS is not documented in the review.

B. Fibrotic Complications

Dr.Boehm reviewed the sponsor's analyses for fibrotic complications, to include valvulopathy. There were no worrisome findings, but Dr.Boehm notes that this is not completely reassuring due to 1) the lack of prospective intensive monitoring for these events, and 2) the relative lack of the longterm data that would be required to fully assess this risk. Standard language for possible fibrotic complications should be included in labeling.

C. Pathologic Gambling

There were no AEs of pathologic gambling observed. However, the ascertainment of the event without targeted questioning might be unlikely. Therefore, the safety review team suggests that further studies with rotigotine should incorporate specific questioning about this phenomenon into the protocol in order to better assess the possibility that the drug could increase the propensity to this behavior.

Laboratory Data

The sponsor states that there are no clinically relevant trends in the laboratory data. Dr.Marc Stone reviewed the laboratory data. For rotigotine treated patients, there was an average decline in hemoglobin of 0.1 gms/dL during the course of clinical trials. Analyses for treatment-emergent abnormally low values for hemoglobin showed that 8% of both rotigotine and ropinirole patients met this threshold versus 5% for placebo patients. The numbers of extreme outliers are small, but still with a slight excess on drug. The safety team has requested more information on the extreme outliers for lab data. This seems like a reasonable next step to investigate this issue.

For the lab data from the early PD experience, Dr.Stone further analyzed some very small mean changes observed in hemoglobin and albumin. He fit the changes in these (and several other) lab values to a linear model which predicted that the values would continue to decline if patients were followed out in time over several years or more.

Dr.Stone's conclusion is that there is a real possibility of serious harm if the drug is used in large numbers of patients for long periods of time. In fact, this is only a hypothetical possibility based on the modeling exercise that Dr.Stone has undertaken with several lab analytes. The actual changes observed under the conditions of the clinical trials were extremely small, so small that they would be considered of trivial significance by clinicians. Given that multiple analytes were examined, there is also a real possibility that these small findings occurred by chance. To use the slopes taken from his predictive model in a regulatory decision would, of course, set a new standard for approvability, a standard that has not been discussed or adopted by a wider audience.

Dr.Racoosin, the Safety Team Leader, has proposed asking the sponsor for lab data from trials in advanced PD (trials where larger doses of rotigotine are possible) and examining that data in a similar fashion. See her memo for a more detailed discussion of Dr.Stone's analyses and recommendations for further follow-up.

Additionally, Dr.Stone notes that data on serum bicarbonate was not collected in phase 3 trials; it was collected in Study 506.

Blood Pressure

Dr.Stone reviewed the vital sign data. He has characterized the effects of rotigotine on blood pressure and pulse and made recommendations for labeling. Rotigotine did not seem to have an impact on orthostatic hypotension, but it did show the potential to cause both increases and decreases in BP.

Effects on the QT Interval

Effects of rotigotine on the hERG channel were seen with an IC50 of 150nM, suggesting the possibility that rotigotine might prolong the QT interval in patients.

Currently, the sponsor is conducting a formal QT study, incorporating a placebo-control, and active-control, and exploring doses higher than 18mg (doses as high as 54mg are planned). There have been recent discussions between the sponsor and the division about this protocol. The division has suggested that the sponsor also explore doses lower than 18mg (to fully characterize the dose-response curve) and has commented on the planned analyses of the data. The results of this study will, of course, not be available during the current review cycle.

In the meantime, Dr.Stone has reviewed data accrued across the rotigotine development program bearing on the QT interval. In Studies 512 and 513, EKGs were collected at baseline and at the end of the maintenance period. EKGs in these studies were all centrally read in a blinded fashion per FDA's request at a pre-NDA meeting. No effect on QT interval is suggested from these EKGs. One Phase 2 study, Study 591, randomized patients to 2 different dose-escalation regimens, with both groups advancing to a maximum dose of 54mg. Dr.Stone found no significant change from baseline QT interval in this study for the small group of patients that achieved the highest doses (including 54mg).

There was one dedicated EKG study. That study did not include a positive control, making the overall negative results for rotigotine at the doses tested difficult to interpret. Also, EKGs in this study were possibly not collected at timepoints that approximated Tmax (per Dr.Kavanagh's ClinPharm Review).

At this point in time, then, there is a signal from the hERG channel assay suggesting the possibility that rotigotine will prolong the QT interval in patients. However, in the EKG data from the clinical trials, no effect on QT interval has been observed. A QT study to address the issue more comprehensively is currently ongoing.

In controlled trials in early PD, QT prolongation was reported as an AE in 0.3% (1) of placebo patients versus 1.2% (8) of rotigotine patients. This differential is not noted for the later PD studies.

DMETS Consult

The Division of Medication Errors and Technical Support (DMETS) was consulted in November 2003 for a review of the proposed proprietary name, Neupro. DMETS had no objection to the name Neupro based on the potential for confusion with other approved drug products at that time. (Another proposed name was discouraged.) DMETS did have other comments on labeling for the product, to include a recommendation that labeling express the actual dose released per 24 hours, not the dose contained in the patch.

The reason for this request is the anticipated future use of generic products. Generic patches are not required to contain the same amount of drug as the innovator; they are only required to release the same amount per 24 hours. In the future, there could be confusion if different patches were bioequivalent, but had different strengths expressed on their labels.

Given the passage of time, DMETS was recently re-consulted on the acceptability of the name Neupro. Their response is still pending.

Conclusions

The sponsor has provided evidence from 3 controlled trials demonstrating the efficacy of the rotigotine patch in the treatment of early PD. Studies in advanced PD are ongoing.

The cardiac rhythm disturbances in the IV phase 1 studies continue to concern me. In particular, the evolution of ventricular tachycardia in one patient during IV infusion of rotigotine appeared to be associated with plasma levels of rotigotine that will be experienced by patients using the patch. I agree with Dr.Racoosin, the Safety Team Leader, that a more comprehensive review of the potential of rotigotine to cause ventricular arrhythmias is warranted. It also seems appropriate to collect more data on cardiac rhythm in additional studies.

Per the DMETS consult, product packaging and labeling should express the dose as dose-delivered, not dose-included in patch. This will prevent confusion in the marketplace once generics become available. Note that this review has not used this convention.

Recommendations

I recommend that an Approvable Letter be sent asking for the following:

1. More information about the marked outliers for laboratory abnormalities.

2. A more comprehensive review of cardiac arrhythmias, as outlined in Dr.Racoosin's memo.

3. Consideration for submitting the formal QT study ___ , specifically including holter monitor data on rhythm disturbances.

There may be additional requests for the sponsor from the chemistry and pharm/tox reviews, once they are completed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Feeney
2/21/2006 09:46:02 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
Safety Team Leader Review of Selected Safety Issues in the
NDA Safety Database

NDA: 21-829
Drug: rotigotine (neupro®)
Route: transdermal patch
Indication: early Parkinson's disease
Sponsor: Schwarz Biosciences
Action Date: 2/28/06

1 Background

Drs. Boehm, Stone, and Hughes have provided a thorough review of the safety experience with rotigotine. In this memo I will address only selected safety issues that require additional discussion.

As described in more detail in the primary safety review, Schwarz (the sponsor) combined various studies together to produce patient pools of interest. These pools are described in tabular form in Appendix 4.1 of this review. The pools that I will primarily refer to are pool S1, consisting of double-blind data from all controlled phase 2/3 trials with treatment durations ≥3 months in patients with early-stage Parkinson's disease, and pool S3, consisting of data from all phase 2/3 trials (double-blind and open-label) in patients with early-stage Parkinson's disease. Appendix 4.2 contains a tabular summary of the important aspects of the trials included in pool S3 (which also encompasses pool S1).

2 Selected safety issues in the rotigotine NDA database

2.1 Cardiovascular rhythm disorders

In the early-stage PD studies (pool S3), two rotigotine-treated patients died (0.2%), two ropinirole-treated (active control) patients died (0.9%)[1], and no placebo-treated patients died. The two deaths in rotigotine-treated patients, occurring during open label extensions, were characterized as sudden deaths, one witnessed and one unwitnessed. The witnessed sudden death occurred 11 days into the open label period in a 50 year old male who took rotigotine during the double blind (DB) period (modal dose 18mg) and had a history of treatment emergent hypertension and initiation of beta blocker therapy two weeks prior to death. Multiple ECGs conducted during the study did not reveal evidence of QT prolongation (using the Bazett's correction); however, a consultant cardiologist considered ECGs conducted during the controlled portion of the trial as having evidence of posterolateral wall myocardial ischemia. The unwitnessed sudden death occurred after

[1] One ropinirole death was attributed to a suicide; the other was attributed to an MI.

246 days into the open label period (at 18mg/day) in a 57 year old male with a history of diabetes who also had treatment emergent elevation of blood pressure. Bazett's corrected QT intervals (QTcB) were not prolonged on ECGs recorded during the trial. Of the remaining deaths in rotigotine-treated patients through the safety update (n=5), one other had a potential cardiac cause. A 74 yo woman in a DB advanced PD trial experienced abdominal pain on day 53 of rotigotine 18mg/day. She attributed the pain to her gall bladder. She was found dead in bed the next day by her husband. A post-mortem needle aspiration revealed passive congestion of the lungs and myocardial fibrosis. She was noted to have treatment-emergent hypertension (highest SBP 170, highest DBP 80; not recorded as an AE), and ECGs conducted during the trial showed incomplete RBBB, displacement of the R/S transition, and T wave abnormalities. Her highest QTcB during the trial was 443 msec; she was not known to have a history of cardiac disease.

Several cardiac arrhythmia SAEs occurred in rotigotine treated patients. The full safety review (FSR) presents narratives for particular cases in section 7.1.2. Cardiac arrhythmia related adverse events also led to discontinuation from early PD, advanced PD, and clinical pharmacology trials. Narratives for specific cardiac arrhythmia AEs leading to discontinuation are located in section 7.1.3.2 of the FSR. I refer the reader to that document for the details of these narratives. What is notable is that several of these AEs occurred in clinical pharmacology studies during which cardiac monitoring occurred. In several cases, rotigotine treatment was associated with increases in atrial and ventricular premature contractions, which then abated when rotigotine treatment was discontinued.

Preclinical studies suggested that rotigotine may prolong cardiac repolarization. The clinical pharmacology studies that the sponsor has conducted to specifically examine the capability of rotigotine to prolong cardiac repolarization have not demonstrated an increased risk. However, as Dr. Stone points out in his review of that data, the studies were not optimally designed to identify that risk, should it be present. In the clinical studies, some rotigotine-treated patients experienced QT prolongation SAEs and/or discontinued rotigotine treatment for QT prolongation. No specific adverse event narratives documented torsade de pointes; however, one patient experienced a "ventricular arrhythmia" (no additional description provided) that was treated with magnesium (a possible treatment for torsade de pointes). The protocol for a "thorough" QT study has recently been agreed upon between DNP and Schwarz. This study should provide the necessary data to assess the risk of rotigotine-associated QT prolongation. It should be noted that rotigotine-induced QT prolongation, should it occur, would not necessarily explain the ventricular ectopy or certain kinds of ventricular arrhythmia that have been described in rotigotine-treated patients, but that does not rule out the possibility of a another arrhythmic process occurring.

The difficulty in assessing the frequency of cardiac arrhythmia from AEs in the rotigotine development program stems from two problems:

- The way in which the sponsor has chopped up the population into small segments
    - Early PD, advanced PD, restless legs syndrome, clinical pharmacology, etc
- The variety of preferred terms that may be used to describe a cardiac arrhythmia

- Arrhythmia ventricular, tachycardia ventricular, palpitations, ECG abnormal, premature atrial and ventricular contractions, etc.

The sudden deaths in rotigotine-treated patients that occurred in the PD trials, along with the SAEs and discontinuations related to cardiac arrhythmia in the rotigotine development program require that this issue be examined in a more comprehensive way.

Because these arrhythmia events are occurring relatively rarely in the various trials, I suggest that the divisions between indication-specific groupings be eliminated for the purposes of the comprehensive analysis. Thus all cardiac arrhythmia related AEs should be included from any trial that has been unblinded, regardless of the indication or phase of development. A broad net should be cast to include all potentially cardiac arrhythmia related AEs. For studies that used MedDRA, search terms should include those that fall into the MedDRA Higher Level Group Terms (HLGTs) "Cardiac arrhythmias" and "Cardiac disorder signs and symptoms" (under the Cardiac disorders System Organ Class [SOC]) and the Higher Level Terms (HLTs) "ECG investigations" and "Heart rate and pulse investigations" (under the Investigations SOC, Cardiac and vascular investigations HLGT). If the sponsor identifies other MedDRA preferred terms (PTs) that would identify cardiac arrhythmia AEs, then those should be included as well. For studies that used WHO-ART, search terms should be used that correspond to the categories listed above for MedDRA.

Narratives for the events should be written to include pertinent information such as cardiac history, cardiac risk factors, pre-existing medications and medications initiated during study drug treatment, results of baseline and on-treatment ECGs, details of the adverse event, etc. The narratives, as well as the original ECGs, should then be examined by a cardiologist who is blinded to the patient's treatment assignment and who has not been previously involved with evaluating the cardiac AEs in the rotigotine development program. The blinded cardiologist should then recode the AEs to reflect the condition most accurately described by the narrative and ECGs. For example, an AE such as "ECG abnormal" or "Arrhythmia" can be assigned to a more specific PT. The frequencies of the various newly assigned PTs should then be calculated by treatment group. Additional analyses should also be conducted to look for a dose-response relationship and/or a relationship to duration of treatment. It would be useful at the time we get this comprehensive analysis of cardiac arrhythmia, to also have the results of the "thorough" QT study to examine.

One additional way to get more information about the potential relationship between rotigotine and ventricular ectopy/arrhythmia would be to add Holter monitoring to the "thorough" QT study. It would be reasonable to do a 24 hour reading at baseline, at a dose in the midrange (18-27 mg/day), at a dose in the high range (45-54 mg/day), and at the visit two weeks after the end of the trial (to look for the effect of dechallenge).

2.2 Laboratory abnormalities

In section 7.1.7.4 of the FSR, Dr. Stone explicates his additional analyses of the laboratory data in pool S1. He conducted a mixed effects linear model to look for differences in trends over time between subjects receiving rotigotine and those receiving

placebo. This analysis identified hemoglobin and albumin as having highly statistically significant differences in the slope and intercepts of trends over time between rotigotine and placebo treatment arms.

Due to the highly statistically significant differences in the treatment arms for these analytes, Dr. Stone conducted additional in-depth analyses.

The reader should note that the sponsor used the international unit g/L. Because the conventional unit is g/dl, these values appear 10-fold greater than would be observed with the conventional unit.

2.2.1 Hemoglobin

The sponsor's outlier analysis for treatment emergent "abnormally low" hemoglobin values showed that 5% of placebo-, 8% of rotigotine-, and 8% of ropinirole-treated patients met this threshold during at least one on-treatment visit. Dr. Stone's analysis of incidence of marked abnormalities at any visit (counted number of abnormal *measurements*, not number of abnormal *patients*), showed an excess of markedly abnormal hemoglobin values in the rotigotine group compared to the placebo group (0.76% vs. 0.45%).

Dr. Stone's more in-depth analyses of hemoglobin showed evidence of a decline for rotigotine subjects when compared to placebo subjects. The overall main effect was estimated as 1.55 g/L (0.16 g/dl); there was evidence of a trend over time of 0.1 g/L per week (0.01 g/dl per week). This was the estimate for the S1 pool; it was driven primarily by study SP513 which had a highly significant p value (SP506 was not statistically significant; SP512 trended towards significance; refer to Table 7.1.7.4.2 of the FSR). The decline appeared linear and did not appear to attenuate with time. A decline was also seen in rotigotine-treated patients in the open label extensions regardless of what treatment group they were in during the DB trial. However, the rate of decline was smaller in absolute terms (0.02 g/L [0.002 g/dl] per week).

Dr. Stone also examined the risk of crossing various thresholds- below normal, >10g/L (1g/dl) drop, >20g/L (2g/dl) drop (see Table 7.1.7.4.4 of the FSR). When the S1 pool is considered, the risk of the rotigotine treated patients crossing each of those thresholds is 3-4 fold that of the placebo group; the elevated risk is statistically significant. For the ">20g/L" threshold, the finding is significant only for the S1 pool (not the individual studies).

In order to get a better sense of whether there were more severe outliers, I asked Dr. Stone to look at hemoglobin drops up to 50 g/L (5 g/dl). The following table summarizes the risk for drops of 10 g/L up to 50 g/L for the S1 pool. The differences observed between treatment groups at the >10g/L and >20g/L thresholds were statistically significant by the Fisher's Exact test. Few patients experienced hemoglobin drops greater than 20g/L.

Threshold	Placebo (N=288)	Rotigotine (N=649)	Ropinirole (N=228)

	n	%	n	%	n	%
>10 g/L	21	7.3%	134	20.6%	28	12.3%
>20g/L	3	1.0%	23	3.5%	1	0.4%
>30g/L	1	0.3%	4	0.6%	0	0
>40g/L	0	0	3	0.4%	0	0
>50g/L	0	0	3	0.4%	0	0

Dr. Stone's additional analyses showed that the decline in hemoglobin was associated with a decline in MCV, suggesting a microcytic anemia; this association was only noted in the open label studies.

2.2.2 Albumin

Dr. Stone's more in-depth analyses of albumin showed evidence of a decline for rotigotine subjects when compared to placebo subjects. The overall main effect was estimated as 0.2 -0.34 g/L (0.02-0.03 g/dl) depending on whether a lag time for an effect was considered; there was evidence of a trend over time of 0.02 g/L per week (0.002 g/dl per week). This was the estimate for the S1 pool; SP513 and SP506 trended towards significance and SP512 was not significant. Additional analyses showed that albumin trended with changes in hemoglobin such that for a change in 1 g/L of hemoglobin, albumin changed 0.2 g/L.

2.2.3 Correlation and Cluster analyses

Given the way in which albumin changed with hemoglobin, Dr. Stone examined the correlations between other analytes and hemoglobin (see Table 7.1.7.4.5 of the FSR). From his clinical perspective, Dr. Stone surmised that the inverse correlations of BUN (without change in creatinine), serum chloride, and urine pH with hemoglobin signaled physiologic changes suggestive of decreased renal perfusion and metabolic acidosis of renal origin. Serum bicarbonate was not measured with any regularity in the rotigotine development program, so there is no way to further assess systemic acid-base balance.

Dr. Stone conducted a cluster analysis to identify patients with the pattern of analytes described above. When he prespecified clusters based on changes in hemoglobin, albumin, chloride, and BUN, a group of 64 patients was identified that had declines in hemoglobin and albumin, and increases in chloride, BUN, and urine pH. Among these 64 patients, 54 were rotigotine-treated and 10 were placebo-treated (OR 2.5 [95% CI 1.2-4.9]). Further analysis showed that the rotigotine cluster of 54 patients primarily accounted for the mean declines in hemoglobin over time (see Figure 7.1.7.4.4).

2.2.4 Team Leader comment

Dr. Stone concluded on the basis of his in-depth laboratory analyses that "there is a strong association between exposure to rotigotine and declines in blood hemoglobin and serum albumin. These changes, along with a decline in mean cellular volume appear to be part of a single process, occurring concurrently within the same individuals." He goes on to attribute this process to an anemia of chronic disease or a chronic inflammatory process. Dr. Stone points out that no one suffered serious outcomes from anemia in the rotigotine development program as presented in the NDA safety database through the

safety update[2]; however, he expresses concern that in a sicker patient population (such as the one who will likely take the drug after it is marketed), the small changes he identified could be more problematic. Ultimately, Dr. Stone concludes that adequate labeling can not be written until the effects of rotigotine on blood hemoglobin and albumin are better understood. He recommends that more extensive study of hematopoietic parameters must be conducted prior to approval of rotigotine.

Dr. Stone performed additional statistical analyses to further characterize the declines in hemoglobin and albumin that were suggested by the sponsor's mean change and outlier analyses. Dr. Stone's methodological approach has not generally been applied to NDA safety databases, at least not that I have observed in nine years in DNP (formerly DNDP). It seems to me that there are two questions at hand- first, is the finding real- or given the multiple comparisons- is the hemoglobin decline a chance finding? In some cases, laboratory changes that are statistically significant in the S1 pool are driven by marked changes in only one of the trials. This inconsistency across trials supports the possibility that some of the significant laboratory findings may have occurred by chance.

The second, and likely more challenging, question follows: if the finding is real, what is the potential harm associated with very small observed changes? Dr. Stone notes that the small changes are averages, and some patients are likely to experience more marked changes. He has, in fact, demonstrated just that – identifying a cluster of patients who appear to account for the bulk of the mean decline in hemoglobin. However, even in those most severely affected patients, the mean decline is 11.8 g/L (1.2 g/dl).

In a recent discussion of the "thorough" QT protocol, DNP requested that additional laboratory data be collected at baseline, at the highest doses, and two weeks after the end of the study. Reticulocyte count, serum ferritin, sedimentation rate, and urine hemoglobin will supplement the CBC data. Because this trial is relatively short (about 7 weeks) and relatively small (about 80 patients), it is unclear whether the laboratory data will be informative. Another potentially useful source of information is the laboratory data collected during the advanced PD studies. Although some adverse event data from these trials was included with the safety update, the laboratory data was not. Because the patients participating in the advanced PD trials were older, likely with more comorbidities, and treated at higher doses, if there is a truly a relationship between rotigotine, anemia and the other laboratory changes noted in the early-stage PD database, it should be evident in this database.

Dr. Stone notes that it is important to determine whether the reduction of hemoglobin and albumin are reversible with discontinuation of rotigotine. Even in the face of small changes, I agree that this would be useful information. It appears that there are laboratory data corresponding to the de-escalation and follow-up treatment periods. The sponsor should be able to examine each individual patient's laboratory data and treatment record to determine whether declines during treatment recover during the de-escalation and follow-up periods.

---

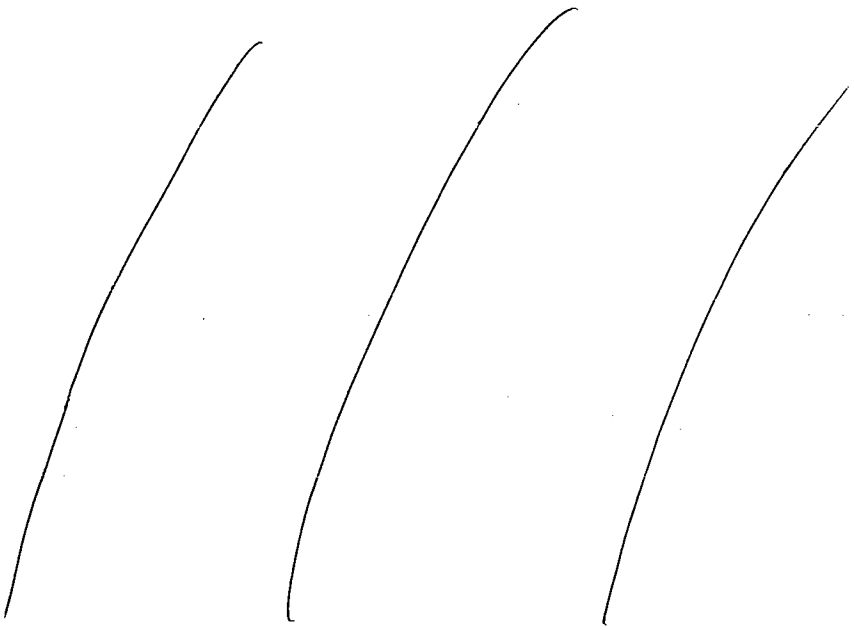
[2] There were eight early PD rotigotine subjects with treatment emergent anemia AEs (0.7%, 8/1093) through the safety update (one SAE).

Requests regarding the laboratory data, as described above, should be included in the approvable letter.

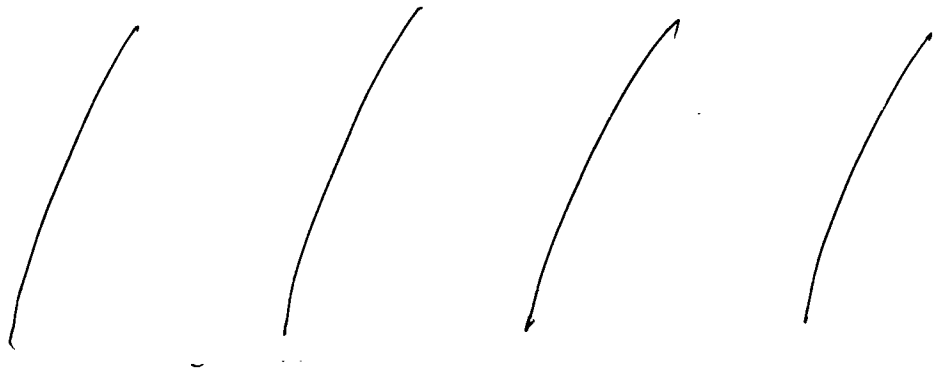
2.3 Sleep attacks

The earliest published reports of sleep attacks (sometimes referred to as "sudden uncontrollable somnolence" or "sudden onset sleep") associated with the dopamine agonists (both ergot and non-ergot) appeared in journals such as Neurology[3], Movement Disorders[4], and Lancet[5] in 1999 and 2000. Additional case series and observational studies have been subsequently published. Rotigotine is the first dopamine agonist development program to prospectively identify sleep attacks as an AE of interest. As such, we have a clear estimate of the frequency of sleep attacks with rotigotine treatment. In the pool S1 studies, 1.4% of rotigotine and 1.9% of ropinirole subjects experienced sleep attacks compared to no placebo subjects. Four sleep attacks were SAEs, most occurring while driving. The incidence of sleep attacks with rotigotine is comparable to the incidence observed with the active control ropinirole, thus it doesn't appear unusual in its tendency to induce sleep attacks among the dopamine agonist class; however, it is crucial that rotigotine be labeled prominently to warn of this potentially life-threatening risk.

3 Labeling



[3] Frucht S et al. Falling sleep at the wheel: motor vehicle mishaps in persons taking pramipexole and ropinirole. *Neurology* 1999; 58: 1908-1910.
[4] Hauser RA et al. Pramipexole-induced somnolence and episodes of daytime sleep. *Movement Disorders* 2000; 15: 658-663.
[5] Schapira AH. Sleep attacks (sleep episodes) with pergolide. *Lancet* 2000; 355: 1332-1333.



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4 Appendices

4.1 Study pools employed by Schwarz in the safety analysis

Pool	Description of pool	Trials included in pool	Number of rotigotine-treated subjects
Pool S1	Primary pool; consists of double-blind data from all controlled phase 2/3 trials with treatment durations ≥3 months in patients with early-stage Parkinson's disease	SP506;[6] SP 512 (DB portion); SP513 (DB portion)	649
Pool S2	double-blind data from all controlled phase 2/3 trials in patients with early-stage Parkinson's disease	SP506; SP512 (DB); SP513 (DB); SP534 (Parts 1 and 2); SP540; SP535	708
Pool S3	data from all phase 2/3 trials (double-blind and open-label) in patients with early-stage Parkinson's disease	SP506; SP512 (DB and OL); SP513 (DB and OL); SP534 (Parts 1 and 2); SP540; SP535; SP630	1093
Pool S4	double-blind data from all phase 3 trials in patients with early-stage Parkinson's disease	SP512 (DB) and SP513 (DB)	396
Pool S5	data from phase 3 trials in patients with early-stage Parkinson's disease treated at least once in open-label	SP512 (DB and OL) and SP 513 (DB and OL)	276
Pool S6	open-label data from phase 3 trials in patients with early-stage Parkinson's disease treated at least once in open-label	SP512 (OL) and SP513 (OL)	596
Pool P11	Data from healthy subjects in phase 1 trials	SP502; SP503; SP581; SP596; SP606; SP610; SP626; SP627; SP629; SP670; SP673; SP717; SP718; SP671 (data from healthy subjects only); SP672 (data from healthy subjects only)	547
Pool P12	Data from patients with hepatic or renal impairment in phase 1 trials	SP671 (data from patients with hepatic impairment only); SP672 (data from patients with renal impairment only)	33
Pool AS1	Data from trials in patients with advanced-stage Parkinson's disease	SP533; SP591; SP511; SP 650 (DB and OL)	589
Pool RLS	Data from trials in patients with restless leg syndrome	SP666; SP628l; SP 709; SP710	389

[6] The sponsor noted differences in the design of trial SP506 compared to SP512 and SP513. They stated that differences in dosing and patch placement protocols may have affected the appropriateness of pooling data from SP506 with data from SP512 and SP513. In SP506, the subjects in the two lowest dose groups (4.5 mg/day and 9 mg/day) did not receive higher doses at any point during the trial. In contrast, rotigotine doses were titrated higher in SP512 and SP513. In SP506, rotigotine patches were applied to the upper abdomen only. In SP512 and SP513, rotigotine patches were rotated between abdomen, thigh, hip, flank, shoulder, and upper arm.

4.2 Tabular summary of characteristics of S3 studies

(See subsequent pages)

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Protocol No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
Reports of Efficacy and Safety Trials							
Trial Reports of Controlled Clinical Trials Pertinent to the Claimed Indications							
SP534 Part 1/ US	Evaluate safety and tolerability of fixed doses	Double-blind, placebo-controlled, parallel, fixed dose, dose ranging	Rotigotine/ 9.0mg and 13.5mg/ silicone patch	4 weeks	2 placebo, 10 rotigotine/ 10 M/ 2 F	69 years (45-83)	Complete/ Full
SP534 Part 2/ US	Evaluate safety and tolerability of dose escalation	Double-blind, placebo-controlled, parallel, dose escalation	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch	4 weeks	2 placebo, 10 rotigotine/ 8 M/ 4 F	Rotigotine: 78 (70-85) Placebo: 71 (67-75)	Complete/ Full
SP535/ US	Evaluate safety and tolerability	Double-blind, placebo-controlled, dose escalation	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch	4 weeks	2 placebo, 8 rotigotine/ 7 M/ 3 F	Rotigotine: 53 (38-67) Placebo: 53 (36-70)	Complete/ Full

Protocol No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
SP506/ Canada, Europe, India, South Africa, Ukraine, US	Evaluate efficacy, safety and tolerability	Double-blind, randomized, placebo-controlled, parallel, dose response	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch	12 weeks	64 placebo, 265 rotigotine/ 62% M/39% F	60 years (33-83)	Complete/ Full
SP512 Part I/ Canada, US	Evaluate efficacy, safety, and PK compared to placebo	Double-blind, randomized, placebo-controlled, optimal dosing	Rotigotine/ 4.5mg, 9.0mg, 13.5mg/ silicone patch	27 weeks	96 placebo, 181 rotigotine/ 65% M/35% F	63 years (32-86)	Complete/ Full

Protocol No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
SP513 Part I/ Europe, Israel, New Zealand, South Africa, Switzerland Australia	Evaluate efficacy, safety, and PK of rotigotine compared to placebo and ropinirole	Double-blind, randomized, placebo- and active-controlled, double-dummy, optimal dosing	Rotigotine/ 4.5mg, 9.0mg, 13.5mg, 18.0mg/ silicone patch Ropinirole/ 0.75-24.0mg/ oral	up to 37 weeks	118 placebo, 215 rotigotine, 228 ropinirole/ 58% M/ 42% F	61 years (30-86)	Complete/ Full
Trial Reports of Uncontrolled Clinical Trials							
SP512 Part II[d] (SP702)/ Canada, US	Evaluate long-term safety	Open-label	Rotigotine/ Year 1=up to 13.5mg, Years 2-4=up to 36.0mg/ silicone patch	up to 4 years	213 rotigotine/ 68% M/32% F	63 years (33-86)	Ongoing/ Interim

Protocol No./ Country or Region(s)	Objective(s) of Trial	Trial Design and Type of Control	Test Product(s)/ Dosage Regimen[a]/Route of Administration	Duration of Treatment	Number of Randomized Subjects for Each Treatment/ M/F	Mean Age of Subjects/ (Range)	Trial Status/ Type of Report
SP513 Part II[d] (SP716)/ Europe, Israel, New Zealand, South Africa, Switzerland Australia	Evaluate long-term safety	Open-label	Rotigotine/ Year 1=up to 18.0mg, Years 2-4=up to 36.0mg/ silicone patch	up to 4 years	372 rotigotine/ 61% M/39% F	61 years (30-82)	Ongoing/ Interim
SP540/ Europe, South Africa	Evaluate efficacy and safety	Single-blind[e], multi-center	Rotigotine/ maximum tolerated dose up to 18.0mg/ silicone patch	28 days	31 placebo and rotigotine/ 42% M/58% F	61 years (40-78)	Complete/ Full

4.3 Labeling proposal

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/s/

Judith Racoosin
2/16/2006 11:49:31 AM
MEDICAL OFFICER

CLINICAL SAFETY REVIEW

Application Type	NDA
Submission Number	021829
Submission Code	N 000 AM
Letter Date	9/13/05
Stamp Date	9/14/05
PDUFA Goal Date	2/28/06
Reviewers' Names	Marc Stone, M.D., Alice Hughes,M.D., Gerard Boehm, M.D. MPH
Review Completion Date	2/15/06
Established Name	Rotigotine
(Proposed) Trade Name	Neupro
Therapeutic Class	Dopamine Agonist
Applicant	Schwarz Biosciences
Priority Designation	S
Formulation	Transdermal Patch
Indication	Early Parkinson's Disease

1 EXECUTIVE SUMMARY 4
1.3.3 Safety 4
7 INTEGRATED REVIEW OF SAFETY 8
7.1 Methods and Findings 8
7.1.1 Deaths 8
7.1.2 Other Serious Adverse Events 12
7.1.3 Dropouts and Other Significant Adverse Events 21
7.1.3.1 Overall profile of dropouts 21
7.1.3.2 Adverse events associated with dropouts 22
7.1.5 Common Adverse Events 33
7.1.5.1 Eliciting adverse events data in the development program 33
7.1.5.2 Appropriateness of adverse event categorization and preferred terms 33
7.1.5.3 Incidence of common adverse events 34
7.1.5.4 Common adverse event tables 34
7.1.5.5 Identifying common and drug-related adverse events 40
7.1.5.6 Additional analyses and explorations 40
7.1.6 Less Common Adverse Events 53
7.1.7 Laboratory Findings 55
7.1.7.1 Overview of laboratory testing in the development program 55
7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values 56
7.1.7.3 Standard analyses and explorations of laboratory data 56
7.1.7.3.1 Analyses focused on measures of central tendency 56
7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal 56
7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities 56
7.1.7.4 Additional analyses and explorations 57
7.1.7.5 Overview of vital signs testing in the development program 69
7.1.7.6 Selection of studies and analyses for overall drug-control comparisons 70
7.1.7.7 Standard analyses and explorations of vital signs data 70
7.1.7.7.1 Analyses focused on measures of central tendencies 70
7.1.7.7.2 Analyses focused on outliers or shifts from normal to abnormal 71
7.1.7.7.3 Marked outliers and dropouts for vital sign abnormalities 75
7.1.7.8 Additional analyses and explorations 75
7.1.7.8.1 Analyses focused on measures of central tendencies 75
7.1.7.8.2 Analyses focused on outliers or shifts from normal to abnormal 85
7.1.9 Electrocardiograms (ECGs) 89
7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results 89
7.1.9.2 Selection of studies and analyses for overall drug-control comparisons 91
7.1.9.3 Standard analyses and explorations of ECG data 97
7.1.9.3.1 Analyses focused on measures of central tendency 97
7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal 100
7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities 103

7.1.10 Immunogenicity 109
7.1.11 Human Carcinogenicity 109
7.1.12 Special Safety Studies 110
7.1.13 Withdrawal Phenomena and/or Abuse Potential 116
7.1.14 Human Reproduction and Pregnancy Data 117
7.1.15 Assessment of Effect on Growth 117
7.1.16 Overdose Experience 118
7.1.17 Postmarketing Experience 118
7.2 Adequacy of Patient Exposure and Safety Assessments 118
7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and 118
Extent of Exposure) Used to Evaluate Safety 118
7.2.1.1 Study type and design/patient enumeration 118
The table below summarizes overall exposure to the rotigotine silicone patch, which is the formulation proposed for marketing, through July 1, 2004. 119
7.2.1.2 Demographics 121
The following table summarizes demographic data for pool S3, which includes all data from double-blind and open-label studies in patients with early-stage Parkinson's disease: 121
7.2.1.3 Extent of exposure (dose/duration) 123
7.2.1.3.1 Exposure in patients with early-stage Parkinson's disease 124
7.2.1.3.2 Exposure in phase 1 studies 126
7.2.1.3.2 Exposure in patients with advanced Parkinson's disease and restless leg syndrome 126
7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety 127
7.2.2.1 Other studies 127
7.2.2.2 Postmarketing experience 127
7.2.2.3 Literature 127
7.2.3 Adequacy of Overall Clinical Experience 128
7.2.4 Adequacy of Special Animal and/or In Vitro Testing 129
7.2.5 Adequacy of Routine Clinical Testing 130
7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup 130
7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug 130
and Particularly for Drugs in the Class Represented by the New Drug; 130
Recommendations for Further Study 130
7.2.8 Assessment of Quality and Completeness of Data 131
7.2.9 Additional Submissions, Including Safety Update 132
7.3 Summary of Selected Drug-Related Adverse Events, Important 132
Limitations of Data, and Conclusions 132
7.3.1 Application Site Reactions 132
7.3.2 Nausea and Vomiting 132
7.3.3 Sleep Attacks and Sleep Disturbances 133
7.3.4 Hallucinations 133
7.3.5 Effect on Vital Sign Parameters 133
7.3.6 Effect on QT 133
7.3.7 Effect on Lab Parameters 134
7.4 General Methodology 134

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence 134
7.4.1.1 Pooled data vs. individual study data 134
7.4.1.2 Combining data 135
7.4.2 Explorations for Predictive Factors 135
7.4.2.1 Explorations for dose dependency for adverse findings 135
7.4.2.2 Explorations for time dependency for adverse findings 136
7.4.2.3 Explorations for drug-demographic interactions 136
7.4.2.4 Explorations for drug-disease interactions 136
7.4.2.5 Explorations for drug-drug interactions 136
7.4.2.6 Explorations for drug-alcohol and drug-tobacco interactions 137
7.4.3 Causality Determination 137
APPENDICIES **138**

1 Executive Summary

1.3.3 Safety

Schwarz captured adverse event, vital sign, laboratory data and ECG data during their development program studies and conducted special safety studies examining skin sensitivity and effects on cardiac repolarization.

Schwarz identified 2,651 subjects exposed to the rotigotine silicone patch[1]. Five hundred eighty subjects were exposed in Phase I trials, 1093 in early-stage Parkinson's disease (PD) trials (intended indication), 589 in advanced-stage PD trials, and 389 in Restless Legs syndrome trials.

The total number of subjects exposed to rotigotine at doses greater than or equal to those proposed for clinical use is slightly less than 1,500 subjects recommended in the International Conference on Harmonization (ICH) guidelines for exposure to a chronicly administered drug. Schwarz considers 9.0 mg/day to be the minimal effective dose for early stage PD and proposes titrating to maintenance doses of 13.5— − mg/day. Schwarz identified 1,419 subjects exposed to a rotigotine dose of at least 9mg/day and 918 subjects exposed to a rotigotine dose of at least 13.5mg/day.

The number of subjects exposed to rotigotine for at least 6 months and for at least 12 months met ICH exposure guidelines. Across all indications, 1,000 subjects were exposed to rotigotine for at least six months and 665 subjects exposed for at least 1 year to rotigotine.

Through the Safety Update, for the early-stage idiopathic PD studies (intended indication) Schwarz identified 1,093 subjects exposed to rotigotine. These subjects had a cumulative exposure of 979 person years. Five hundred seventy-five early-stage PD subjects were exposed for at least 6 months and 486 were exposed for at least one year. For these 1,093 subjects the most common mean daily doses were 13.5 to<18mg/day (40%, 439) and 9 to <13.5mg/day (40%, 439). For the 575 subjects exposed for at least 6 months, the most common mean daily doses were 13.5 to<18mg/day (55%,

[1] Formulation intended to be marketed

318) and 9 to <13.5mg/day (39%, 222). For the 485 subjects exposed for a year, the most common mean daily doses were 13.5 to<18mg/day (54%, 263) and 9 to <13.5mg/day (40%, 193).

Through the Safety Update, seven rotigotine exposed subjects died. Two deaths occurred in early-stage PD subjects, both sudden deaths. Five deaths occurred in advanced-stage PD subjects, and the causes of death were cerebrovascular accident, unexplained, pneumonia and sepsis, and suicide (2). One of the suicides occurred 95 days after last rotigotine exposure.

In early-stage PD subjects, serious adverse events (SAEs) were reported by 12% (132/1093) of rotigotine subjects and the most common SAEs were accident (1.2%, 13/1093), surgical intervention (0.9%, 10/1093), fall (0.6%, 7/1093), application site reaction (0.5%, 6), sleep attacks (0.5%, 5/1093) and myocardial infarction (0.5%, 5/1093). In early-stage PD Phase II/III RCTs, application site reaction (0.5%, 3/649) was the only SAE occurring in at least 0.5% of subjects and more frequently compared to placebo.

Sixteen percent (173/1093) of rotigotine treated subjects in early-stage PD studies discontinued from trials for adverse events. The most common AEs leading to discontinuation were application site reactions (5.2%, 57), nausea (1.9%, 21), somnolence (1.5%, 16), and vomiting (1.2%, 13). In the early-stage PD phase II/III RCTs, application site reactions (rotigotine 5.2%, 34/649; placebo 0/289), nausea (rotigotine 2%, 13/649; placebo 0/289), and vomiting (rotigotine 1.2%, 8/649; placebo 0/289) were the AEs leading to discontinuation of at least 1% of rotigotine subjects.

Eighty-seven percent (945/1093) of early-stage PD subjects reported Adverse Events (AEs). In the phase II/III early-stage PD trials, the following AEs occurred in at least 5% of rotigotine subjects and were at least twice as common compared to placebo: nausea (rotigotine 38%, 244/649; placebo 15%, 43/289), application site reactions (rotigotine 37%, 239/649; placebo 14%, 40/289), vomiting (rotigotine 13%, 81/649; placebo 2%, 6/289), and insomnia (rotigotine 10%, 64/649; placebo 5%, 14/289). Other AEs of interest occurring more frequently among rotigotine subjects compared to placebo include somnolence (rotigotine 25%, 161/649; placebo 16%, 45/289), and hallucinations (rotigotine 2%, 13/649; placebo 1%, 2/289). Sleep attacks occurred in 1.5% (9/649) of rotigotine subjects, 1.8% (4/228) of ropinirole subjects and no placebo subjects. Syncope risk was similar for rotigotine (1.1%, 7/649) and placebo (0.7%, 2/289) subjects and postural hypotension was more common among placebo subjects (3%, 8/289) compared to rotigotine subjects (1.5%, 10/649). Among rotigotine subjects there were no reported AEs of hepatic failure, pancreatitis, aplastic anemia, pancytopenia, agranulocytosis, toxic epidermal necrolysis, Stevens Johnson syndrome, acute renal failure, or anaphylaxis. There was one case of rhabdomyolysis from advanced PD study 650 OL.

The limitations of the available data include the small size of the database, limited long term data, the selected healthy study population, paucity of active comparator data, and the study designs which compromised dose response analyses. Given the relatively small number of exposed subjects, the ability to detect rare rotigotine related events is limited. Lack of substantial long term exposure data limited the ability to examine risk for select events that might occur with some latency such as fibrotic complications. Exclusion criteria that restricted subject participation to individuals that were relatively healthy would likely lead to underestimates of adverse event risks when rotigotine is used

in larger, less healthy populations. All of the data for active comparator ropinirole came from a single study and the ropinirole sample size was relatively small, limiting the robustness of risk comparisons. Optimal dosing and titration designs make dose response analyses for AEs difficult to interpret.

The division requested that Schwarz provide any important omitted evaluations or data (ex. narratives for AEs leading to discontinuations, analyses of malignancies, etc.) identified during the course of the review. There were no outstanding requests at the time of the completion of the safety review.

Application site reactions were very common among rotigotine treated subjects, but led to discontinuation of only a small percentage of users and rarely were serious AEs. Most subjects' reactions resolved following discontinuation of rotigotine. Data from a clinical pharmacology study suggest that sensitization to rotigotine can occur. These application site reactions may limit the ability of patients to continue treatment and have led to recommendations that increase the complexity of use (recommendations to rotate patch site and not reapply to the same site for 14 days). Schwarz provided literature references supporting that application site reactions are seen commonly with other drugs administered by transdermal patch.

One of the most concerning safety issues with rotigotine is the risk of sleep attacks. Sleep attacks or sudden onset of sleep are a somewhat unique adverse event in that they are potentially harmful not only to the treated patient, but depending on the circumstances, to the general public as well. Sleep attacks were reported for 1.3% of the rotigotine treated population overall; in controlled trials, 1.4% of rotigotine subjects and no placebo subjects experienced sleep attacks. This risk seems high but active comparator data from the controlled trials found a risk of sleep attacks of 1.8% for ropinirole. Historical comparisons to NDA data for recently approved dopamine agonists are not useful because sleep attacks were not yet recognized as related to dopamine agonist treatment at the time when ropinirole and pramipexole were being developed, and hence were not prospectively identified as events of concern. In contrast, by the time rotigotine was being developed, sleep attack had been recognized as related to dopamine agonist treatment and Schwarz prospectively designated them as events of special concern.

There is a strong association between exposure to rotigotine and declines in blood hemoglobin and serum albumin. These changes, along with a decline in mean cellular volume, appear to be part of a single process, occurring concurrently within the same individuals. These changes resemble the clinical picture of chronic illness, the anemia of chronic disease and, frequently, a chronic inflammatory process. Although no subjects suffered serious consequences from anemia or hypoalbuminemia during clinical trials, there is no indication that this process is self-limited or easily reversible with the discontinuation of rotigotine. Consequently, there is a real possibility of serious harm if the drug is used in large populations for prolonged periods, particularly in patients with comorbidities involving compromised erythropoietic capacity. In addition, although there was no indication of effects on platelets and leukocytes as widespread as was seen with hemoglobin and albumin, the higher incidence of abnormally or markedly low platelet and leukocyte, particularly monocyte, counts suggest an effect on hematopoiesis that goes beyond erythrocytes.

In order to reasonably assure the safety of rotigotine, the following information is needed:

1. Controlled clinical studies with more extensive monitoring of clinical parameters including iron, transferrin, ferritin, reticulocyte count, white and red cell morphology, erythropoietin, erythrocyte sedimentation rate, C-reactive protein, haptoglobin and urine hemoglobin as well as hemoglobin; hematocrit; red cell indices; absolute and differential white cell counts; albumin and globulin.
2. Continued detailed monitoring during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and albumin.
3. [redacted]
4. Complete clinical documentation of subjects with markedly abnormal laboratory values.

With regard to vital signs, rotigotine on average increases heart rate and increases the incidence of tachycardia although the frequency of large increases in heart rate does not appear increased. This could be of clinical importance in patients with coronary artery disease or congestive heart failure and should be listed in [redacted] labeling [redacted]

The overall effect on blood pressure is less clear but it appears likely that rotigotine can increase the likelihood of substantial increases or decreases in blood pressure. The Sponsor's proposed labeling [redacted]. However, no significant impact by rotigotine on postural changes in heart rate or blood pressure was observed.

The higher and dose-related incidence of weight loss is likely due to the higher incidence of nausea, vomiting, and anorexia that is already noted in the Adverse Reactions section of the proposed labeling. The higher incidence of weight gain needs additional investigation by the Sponsor: Is it due to improved appetite or to less benign causes such as fluid retention, metabolic alterations or lassitude?

The clinical data provided in this application show little adverse effect of rotigotine on electrocardiographic parameters. There were no dramatic changes in heart rate, rhythm or electrical conductivity attributable to rotigotine. The data, however, are insufficient to conclude that the potential for adverse effects on cardiac electrophysiology suggested by preclinical data does not exist in the clinical setting.

Because rotigotine is associated with an increase in heart rate, the analysis of any possible effect the drug may have on QT interval is obscured due to the results being greatly influenced by the methods used to adjust QT interval for heart rate. Choosing a method based upon whatever method performs best (i.e., reduces any correlation between heart rate and the adjusted QT interval) on subjects when they are not receiving rotigotine (baseline or placebo) is only valid for the distribution of heart rates

used in that sample. The adjustment may not be accurate when applied to a different distribution of heart rates particularly if the average heart rate is significantly higher or lower.

Furthermore, the data provided by the sponsor fails to demonstrate assay sensitivity. Most ECG measurements were made in the presence of relatively low plasma rotigotine levels (<1.0 ng/ml) and almost all have been less than 3.0 ng/ml even though observed levels can exceed 5.0 ng/ml. So while little effect is observed at lower rotigotine levels, insufficient data exist regarding effects at higher but clinically plausible plasma rotigotine levels. Equally important is the need for a positive control to document the safety of rotigotine in subjects known to be susceptible to QT prolongation.

Many of the safety concerns associated with rotigotine use are shared by the other dopamine agonists used for the treatment of Parkinson's disease. Like other dopamine agonists, rotigotine is associated with an increased risk of nausea, vomiting, hallucinations, somnolence, and dizziness. Postural hypotension was reported more frequently for placebo subjects than rotigotine subjects but these same studies also suggested that the risk for postural hypotension with ropinirole was lower compared to placebo, raising questions about the reliability of this finding. Syncope occurred slightly more frequently among rotigotine subjects compared to placebo and less frequently compared to ropinirole although these results do not allow for definitive conclusions regarding the relative risk for this event among treatments.

Without robust head to head studies, there is insufficient data to make definitive safety comparisons among the dopamine agonists used to treat PD. The patch delivery system may offer an advantage in patients having difficulty with taking oral medication but it will also carry the risk of application site reactions and the associated complexity of patch site rotation. To expand the understanding of the safety profile of rotigotine Schwarz should collect additional lab data that were identified above, as well as adverse event data on compulsive behaviors (e.g., pathological gambling, hypersexuality). Although no AEs suggestive of compulsive behaviors were identified in the rotigotine NDA safety database, such events have recently been linked to approved dopamine agonists. Because compulsive behaviors such as gambling may not be recognized as adverse events, specific questioning should be incorporated into study protocols, in order to increase the ability to detect these events.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This safety review was performed by Marc Stone, MD, Alice Hughes, MD, and Gerard Boehm, MD, MPH. Dr. Stone reviewed the laboratory, vital sign and ECG data, Dr. Hughes reviewed the exposure data, and Dr. Boehm reviewed the remaining safety sections.

7.1.1 Deaths

Early Stage Parkinson's disease Indication Phase II/III trials, Pool S3

Through the Safety Update, Schwarz reported 4 deaths from early stage Parkinson's disease trials. Two of the deaths occurred in rotigotine treated subjects (0.2%, 2/1093) and two deaths occurred in subjects treated with ropinirole (0.9%, 2/228) (Safety Update, p.49). The subjects who died while

being treated with rotigotine were enrolled in open label studies. I provide information from the sponsor's narrative summaries for the rotigotine deaths below.

SP513OL/Subject 103717 was a 50-year-old male with medical history of hemorrhoidectomy (1999) and Parkinson's disease. He was dispensed open-label trial medication on [redacted] At the time of the SAE, the subject was taking rotigotine 9.0mg/day. On [redacted] during the titration period of the trial and 11 days after the start of open-label rotigotine, the subject suddenly died. Early in the morning on [redacted] after returning from the bathroom, the subject said a few words to his wife who then noticed he had unusual breathing and then he stopped breathing. She called the emergency team and started cardiopulmonary resuscitation herself. The emergency team found the subject asystolic. Cardiopulmonary resuscitation, including intubation, adrenaline, bicarbonate, and atropine were not successful. Death was declared at 05:00 after a long resuscitation attempt. No autopsy was performed.

The subject received rotigotine (highest dose 18mg, modal dose 18mg) during the double-blind phase. The only AE reported during SP513 Part I was newly diagnosed arterial hypertension. Rotigotine treatment in SP513 Part II was started 11 days prior to the death of the subject. The subject received 4.5mg/day for 7 days. At open-label Visit 2, the dosage was increased to 9.0mg/day. The subject died 3 days following this dose increase. The subject had been referred to his general practitioner on [redacted]. Hypertension was diagnosed by his general practitioner on [redacted], and treatment with atenolol was initiated on that day. Blood pressures and heart rates recorded before and after starting atenolol are shown in the table. The hypertension was reported as an AE during SP513 Part I on 20 Apr 2003.

An expert report from an independent cardiologist was obtained. The cardiologist identified Grade 1 hypertension (WHO criteria) and elevated cholesterol as cardiovascular risk factors. In addition to the negative T waves in leads III and aVF on the 26 Jan 2003 ECG, he noted ST-segment depression in leads aVF, V5 and V6, which he considered pathological and probably indicative of asymptomatic posterolateral wall myocardial ischemia.

Vital signs, laboratory data, and ECGs were recorded during the conduct of SP513DB and SP513OL and summarized in the table.

Date	Treatment	ECG Findings	QTcB (msec)	Blood Pressure (mmHg)	Heart rate (bpm)	Cholesterol (mmol/L)
17 Jul 2002	Screening	T wave decreased in leads III and aVF	392			6.48
24 Jul 2002	Baseline	T wave decreased in leads III and aVF	372 397 388			6.72
11 Aug 2002	Rotigotine 13.5mg/day	T wave decreased in leads III and aVF	387			
25 Aug 2002	Rotigotine 18.0mg/day	T wave decreased in leads III and aVF	405			
30 Oct 2002	Rotigotine 18.0mg/day	T wave decreased in lead III	415			6.11
26 Jan 2003	Rotigotine 18.0mg/day	T wave decreased in lead III	435			6.86
10 Apr 2003	Rotigotine 18.0mg/day	T wave decreased in lead III	397	153/95[a] 146/97[a] 142/93[a] 145/98[a]	80[a] 83[a] 87[a] 86[a]	7.18
[redacted]	Rotigotine 4.5mg/day (OL)			124/83 139/85 136/91 134/88	65 67 67 68	6.95
[redacted]	Rotigotine		384	141/92	68	

	9.0mg/day (OL)			135/93 127/91 134/96	66 71 73	

A Blood pressure and heart rate values were recorded on an unknown date between 10 Apr 2003 and 20 Apr 2003.

NOTE: Cholesterol reference range=0.0 to 5.5mmol/L.

Concomitant medications at onset of the SAE included vitamin C 500mg/day, alfa-tocopherol 500mg/day, atenolol 25mg/day, and amantadine 300mg/day.

SP513OL/Subject 101315 was a 57 year old male with a history of depression, diabetes mellitus, hypertrophy of the prostate, gastric hyperacidity and Parkinson's disease who died suddenly. At the time of the event, the subject was taking rotigotine 18mg/d and had been at this dose level for 246 days. The narrative reported that the event was not witnessed and that attempted resuscitation was unsuccessful. An autopsy was not performed. The narrative noted that the subject's study ECGs were all normal with QTcB ranging from 378-393msec. The subject did have elevated blood pressures (highest 150/100mmHg) at visits 3 and 4. Concomitant medications at the time of the event were amantadine, pyridoxine, and thiamine.

The subjects who died during treatment with ropinirole were participating in controlled trials and the reported causes of death were suicide by hanging (SP513DB/103505) and myocardial infarction (SP513DB/108015).

Deaths in Trials for Other Indications

Advance Stage Parkinson's Disease

Completed Phase II Trials

In the NDA, Schwarz reported no deaths (0/268) in rotigotine treated subjects enrolled in 3 phase II studies (SP533, SP591, and SP511) of advanced stage Parkinson's disease (ISS p.60).

Phase III Trials

In the Safety Update, Schwarz reported that during phase III study SP650 Part I, 2 rotigotine subjects (0.9%, 2/229) and 2 placebo subjects (1.7%, 2/120) died. The causes of death for the rotigotine subjects were cerebrovascular accident (10506), and unexplained death (16220). The placebo deaths were due to pneumonia and cerebrovascular accident (13903), and pneumonia (15203). I summarize information for the rotigotine deaths below.

SP650DB/Subject 10506, an 80 year old female subject with a history of lacunar infarct in basal ganglia, small vessel ischemic disease, hypertension, hallucinations, excessive daytime sleepiness, anxiety, arthritis, insomnia, edema, Parkinson's disease, and multiple other medical problems died following a cerebrovascular accident. The subject was taking rotigotine 18mg/day and had been receiving this dose for 42 days when she awoke with unilateral weakness, mouth drooping, and decreased level of consciousness. A non-contrast CT showed findings consistent with small vessel disease but no evidence of hemorrhage. She was diagnosed with a left cerebral subcortical infarction. Study medication was stopped and the subject was admitted to the hospital. The subject initially showed improvement but then acutely worsened 4 days later (CT demonstrated evolution and progression of the infarction). She required intensive care and blood pressure support, and the health care providers and family decided to transfer the subject to hospice care where she died.

SP650DB/Subject 16220, a 74 year old female with a history of anxiety attacks, excessive daytime sleepiness, depression, cholecystectomy, hypothyroidism, and Parkinson's disease died from unexplained causes. The subject was

taking rotigotine 18mg/day and had been on this dose for 53 days when she experienced abdominal pain that she thought related to her gall bladder. She was found dead in bed the next day by her husband. Resuscitation was attempted but was unsuccessful. Autopsy was limited to needle aspiration and revealed passive congestion of the lungs and mild patchy myocardial fibrosis. The findings were felt consistent with terminal cardiac pump failure as the cause of death. The subject had no known history of cardiac disease. She experienced hypertension during the trial (highest recorded SBP 170, DBP 80, not identified as an AE), and ECGs showed incomplete RBBB, displacement of R/S transition zone, and T wave abnormalities. Her highest recorded QTcB during the study was 443msec. Concomitant medications were carbidopa/levodopa, and levothyroxine.

In the Safety Update, Schwarz reported that through the data cutoff date there have been 3 deaths (1.2%, 3/256) from Study SP650 Part II, the open label extension of the above study (Safety Update, p.125). One of these deaths (11107) was a suicide that occurred 95 days after the subject discontinued from the trial. Because of the time between the end of exposure and the event, I do not discuss the event further. The remaining causes of death were gastrointestinal disorder (11102), and suicide (13101). I summarize information for those deaths below.

SP650 Part II/Subject 11102, a 75 year old male with a history of hypertension, high cholesterol, right hip replacement, Parkinson's disease, and other medical problems, died following an episode of ascending cholangitis, acute cholecystitis and a colo-vesicular fistula. The subject was taking rotigotine 31.5mg at the time of the event and had received 421 days of open label rotigotine. He was admitted to the hospital with abdominal pain that began a day earlier. He was diagnosed with ascending cholangitis, and acute cholecystitis and also had thrombocytopenia and an elevated INR. He was treated with antibiotics and had a slow resolution of thrombocytopenia and coagulopathy. He underwent an ERCP followed by an open cholecystectomy. He was discontinued from the trial. Postoperatively he was diagnosed with a colo-vesicular fistula and underwent a laparotomy and fistula resection. He improved and was discharged to a rehab facility. One month later presented with hypotension, pneumonia, renal failure and septic shock. The subject was administered comfort care measures and subsequently died.

SP650 Part II/Subject 13101 a 72 year old male with a history of COPD, shortness of breath,, femoral and inguinal hernia repairs, Parkinson's disease, and other medical problems, committed suicide 527 days after the start of open label rotigotine. His last rotigotine dose was 27mg and his last rotigotine dose change was an increase to 27mg approximately 53 days prior to attempting suicide. The method of suicide was not identified but the narrative reported that the subject left a note stating that the effort to breathe was no longer worth it. Concomitant medications at the time of death were carbidopa/levodopa, furosemide, potassium, diphenhydramine, triamcinolone, prednisone, and eformoterol.

Deaths in Restless Legs Syndrome Trials

Through the Safety Update, Schwarz reported no deaths for 389 rotigotine treated subjects enrolled in SP628, SP666, SP709, and SP 710, trials for Restless Legs Syndrome (Safety Update, p.139).

Deaths in Other Trials

In the NDA, Schwarz reported no deaths from Phase I studies (n=660) of silicone based rotigotine patches[2] (Summary of Clinical Safety, p.33). There were no deaths from Phase I study SP630 in 70 early stage Parkinson's disease patients (Summary of Clinical Safety, p.31). In the 3 dose range finding intravenous trials (N-0923-001-2601, N-0923-002-01, and N-0923-006-01) in which 29 patients were exposed to rotigotine, there were no deaths reported (ISS p. 30, and study reports). Schwarz did not report any deaths for the 86 rotigotine exposed subjects enrolled in 4 studies (TD-0923-001, TD-0923-002, TD-0923-003, and TD-0923-004) that used prototype patches (ISS, p.32, and study reports).

[2] See section 7.2.1 for a description of the various patches used in the rotigotine development program.

7.1.2 Other Serious Adverse Events

Early Stage Parkinson's Disease Phase II/III Trials, Pool S3

Through the Safety update, Schwarz reported that 12.1% (132/1093) of subjects reported 186 SAEs in Phase II/III early stage Parkinson's disease trials[†] (Safety Update, p.747-754). In the table below I identify the SAEs reported by more than one rotigotine treated subject from these studies.

Body System/Preferred Term	Rotigotine (n=1093)
Any	12.1% (132)
Application Site Disorders	
Application site reaction	0.5% (6)
Autonomic Nervous system	
Hypotension postural	0.3% (3)
Body as a Whole	
Accident NOS	1.2% (13)
Chest pain	0.4% (4)
Influenza-like symptoms	0.3% (3)
Cardiovascular disorders, General	
Syncope	0.3% (3)
Hypertension	0.2% (2)
Gastro-intestinal System Disorders	
Abdominal pain	0.2% (2)
Centr & Periph Nerv Syst Disorders	
Parkinsonism aggravated	0.3% (3)
Confusion	0.2% (2)
Neuropathy	0.2% (2)
Liver and Biliary System Disorders	
Cholecystitis	0.4% (4)
Hepatic enzymes increased	0.2% (2)
Metabolic and Nutritional Disorders	
Hypoglycemia	0.2% (2)
Musculoskeletal Disorders	
Back pain	0.4% (4)
Arthrosis	0.4% (4)
Myo Endo Pericardial & Valve Disorders	
Myocardial Infarction	0.5% (5)
Coronary artery disorder	0.4% (4)
Psychiatric Disorders	
Sleep attacks	0.5% (5)
Hallucinations	0.2% (2)
Depression	0.2% (2)
Somnolence	0.2% (2)
Reproductive Disorders, Male	
Hernia, Inguinal	0.3% (3)
Resistance Mechanism Disorders	
Infection	0.2% (2)
Respiratory System Disorders	
Bronchitis	0.2% (2)
Sleep apnea	0.2% (2)
Secondary Terms	
Surgical Intervention	0.9% (10)
Fall	0.6% (7)

Intervertebral Disc Disorder	0.3% (3)
Urinary System Disorders	
Urinary incontinence	0.3% (3)
Renal carcinoma	0.2% (2)
Urinary tract infection	0.2% (2)
Vascular (Extracardiac) Disorders	
Thrombophlebitis Deep	0.3% (3)
Cerebrovascular disorder	0.2% (2)

[†]In the Safety Update presentation of SAEs for pool S3, Schwarz included data from trial SP630, whereas in the NDA presentation, trial SP630 data were not included in pool S3. Trial SP630 had no SAEs reported.

The following SAEs occurred in one rotigotine subject each from the included trials: abdominal pain, asthenia, chest pain substernal, hernia NOS, edema peripheral, pain, sudden death, hypotension, cardiac failure, ECG abnormal, convulsions, encephalopathy, extrapyramidal disorder, myelitis, tremor, vomiting, gastric ulcer, gastritis, gastrointestinal disorder NOS, gastroenteritis, arrhythmia, QT increased, arrhythmia ventricular, palpitation, tachycardia, tachycardia ventricular, dehydration, arthralgia, avascular necrosis femoral head, bursitis, malformation foot, myalgia, angina pectoris, endometrial neoplasm malignant, hematoma, psychosis, anxiety, anemia, neoplasm NOS, prostatic disorder, herpes zoster, infection bacteria, infection TBC, asthma, coughing, pneumonia, sinusitis, medical procedure, basal cell carcinoma, dermatitis, melanoma malignant, pruritis, rash erythematosus, skin neoplasm malignant, renal calculus, urinary retention, arteriosclerosis renal, and thrombosis carotid (Safety Update pp.747-54).

Early Stage Parkinson's Disease Phase II/III Controlled Trials, Pool S1

In the NDA, Schwarz provided a table that summarized SAEs observed during 3 early Parkinson's disease controlled trials (duration>=3 months). This analysis allowed comparison of risk among rotigotine, placebo and ropinirole treated subjects. In these trials, 7% (44/649) of rotigotine subjects experienced SAEs compared to 6% (17/289) of placebo subjects and 14% (31/228) of ropinirole subjects (Summary of Clinical Safety, p.96). In the following table, I summarize the SAEs that occurred in more than one rotigotine subject and that occurred more frequently in rotigotine subjects compared to either placebo or ropinirole subjects.

Serious Adverse Events, Early Stag Parkinson's Disease Phase II/III Controlled Trials

Preferred Term	Placebo (n=289)		Rotigotine (n=649)		Ropinirole (n=228)	
	%	N	%	N	%	N
Application site reaction	0	0	0.5%	3	0	0
Accident NOS	0	0	0.3%	2	0.4%	1
Chest pain	0	0	0.3%	2	0	0
Neuropathy	0	0	0.3%	2	0	0
Back pain	0	0	0.3%	2	0	0
Sleep attacks	0	0	0.3%	2	0	0
Hernia inguinal	0	0	0.3%	2	1.3%	3
Fall	0.3%	1	0.3%	2	0	0

From ISS table 45.1, pp.1883-9.

SAEs in Trials for Other Indications

Advance Stage Parkinson's Disease

Completed Phase II Trials
Two subjects (20%, 2/10) experienced SAEs during trial SP533 (ISS, p.55). The reported SAEs were inguinal hernia and QTc prolongation. Three subjects (8.8%, 3/34) experienced SAEs during trial SP591 (ISS, p.57). The reported SAEs were falls (n=2, one during pre-treatment period), and hallucinations. In trial SP 511, 3.8% (9/238) of rotigotine subjects and 1.2% (1/84) of placebo subjects experienced SAEs (ISS, p.59). The reported SAEs for rotigotine subjects were application site reaction/blisters, nausea, vomiting, dizziness, diarrhea, blood pressure increased, myocardial infarction, abscess, and dyskinesia.

Phase III Trials
In the Safety Update, Schwarz reported that 19 rotigotine subjects (8.3%, 19/229) and 10 placebo subjects (8%, 10/120) experienced one or more SAEs in trial SP650 Part I (Safety Update, p.125). The SAEs reported by more than one rotigotine subject were cardiac failure (rotigotine <1% [2/229], placebo 0), cellulitis (rotigotine <1% [2/229], placebo 0), and myocardial infarction (rotigotine <1% [2/229], placebo 0)*. The SAEs reported by one rotigotine subject each were myocardial ischemia, atrial fibrillation, chest pain, pain, death, edema peripheral, gait abnormal, hip fracture, fall, rib fracture, uterine leiomyoma, cerebrovascular accident, lumbar radiculopathy, paraesthesia, Parkinson's disease, sleep attacks, cardiac pacemaker insertion, spinal laminectomy, (Safety Update Table 40.1, pp. 505-511).

In study 650 Part II, the open label extension to study 650 Part I, 18 subjects (7%, 18/256) experienced SAEs through the cutoff date (Safety Update, p.130). The SAEs reported by more than one subject were Accident NOS (n=3), cardiac failure (n=2), Parkinsonism aggravated (n=2), and hemorrhage intracranial (n=2). The following SAEs were reported by 1 subject each: asthenia, hydrocephaly communicative, stupor, gastrointestinal disorder NOS, intestinal obstruction, esophageal ulceration, cholecystitis, hepatitis cholestatic, dehydration, hypomagnesaemia, hyponatremia, back pain, muscle weakness, rhabdomyolysis, sleep attacks, suicide attempt, anemia, pneumonia, fall, laboratory test abnormal NOS, cerebrovascular disorder, and thrombophlebitis deep (Safety Update, Study Report Table 5, pp.155-7).

Restless Legs Syndrome
In trials SP628 and SP666, no SAEs were reported (ISS, p.106, Study report SP628, p.58). In trial SP709, one placebo subject (1.8%, 1/55) and four rotigotine subjects (1.4%, 4/285) experienced SAEs. The SAEs reported by rotigotine subjects were accident NOS, constipation, cholecystitis, fall, intervertebral disc disorder, and peripheral ischemia (Safety Update, Study report, pp.117-8). One subject from study SP710 experienced an SAE and that event was neuropathy (Safety Update, p.141).

* These two events were coded by the sponsor separately as myocardial infarction and myocardial infarction acute but are presented together by the reviewer.

SAEs in Other Trials

Schwarz reported two SAEs from Phase I studies (n=660) of silicone based rotigotine patches (Summary of Clinical Safety, p.33). The first SAE (SP503-21) was an episode of dizziness and a fall that resulted in a joint dislocation in a subject who was taking placebo at the time of the event (last exposed to rotigotine 14 days prior). The second SAE (SP673-80125) was an ovarian cyst removal and spontaneous abortion 13 days after discontinuing from a trial for personal reasons. In the three dose range finding intravenous trials (N-0923-001-2601, N-0923-002-01, and N-0923-006-01) in which 29 patients were exposed to rotigotine, there was one reported SAE (Study report N-0923-006-01, p.347-9). The SAE was increased ventricular ectopy (asymptomatic multifocal PVCs, junctional rhythm, and ventricular tachycardia). Schwarz did not report any SAEs for the 86 rotigotine exposed subjects enrolled in 4 studies (TD-0923-001, TD-0923-002, TD-0923-003, and TD-0923-004) that used prototype patches (ISS, p.32, and study reports).

Review of SAE Narratives

In the early Parkinson's disease trials the most commonly reported SAE was accident NOS. I read the narratives for these events and the majority described injuries that occurred following falls. In many cases the causes of the falls were identified (ex. tripped when walking) and did not appear to be due to syncope events.

Application site reactions were the second most frequently reported SAE in the early Parkinson's disease studies. For the most part, the narratives for these events described similar reactions. The reactions were erythematous, edematous, limited to the patch site and were associated pain, burning and pruritis. The events were considered SAEs by the sponsor because they were medically important events. The reactions resolved, sometimes with only patch removal, and in some cases following treatment with antihistamines and/or steroids. I include a summary of an event as an example of these SAEs.

SP512 OL/Subject 12002/82001 a 50 year old white male with Parkinson's disease, intermittent dystonia, and seasonal allergies experienced an application site reaction 37 days after starting open label rotigotine. The reaction was described as erythema limited to the patch site that was elevated/edematous and was without evidence of ulceration or urticaria. The site was painful and pruritic. The event was treated with patch removal and hydrocortisone cream. The subject withdrew from the study for this event.

I identified an application site reaction SAE that was coded to the preferred term skin disorder blisters. This event seemed more severe than the events described above so I summarize the event separately, below.

SP511/ Subject 0509/12047, a 53 year old white male with Parkinson's disease developed blisters at the patch site after 2 and ½ months of rotigotine treatment. Twenty-three days after increasing to 18mg, the subject was noted to have blistering of the skin under 2 patches. The lesions were circumscribed, and limited to the patch size. The lesions were erythematous with erosions, oozing, and crusting. The subject discontinued from the trial on the day the blisters were noticed and the lesions were completely resolved 12 days later. The narrative did not report any other treatment. Concomitant medications at the time of the event were levodopa/carbidopa, and doxycycline.

Four early Parkinson's disease rotigotine subjects and two advanced Parkinson's disease rotigotine subject had sleep attack SAEs. I provide information from the narratives for these events below. Many of these sleep attack events occurred without warning and some occurred while driving.

Sleep attacks Early Parkinson's

SP506/Subject 08901/1726, a 68 year old Caucasian male with a history of Parkinson's disease, insomnia, arthritis, left anterior hemiblock, prostatectomy, and multiple other medical problems was taking rotigotine 13.5mg for 4 days when experienced a sleep attack. The subject fell asleep for 1-2 seconds while driving but did not have an accident. He fell asleep again 4 days later while driving and the episode lasted about 100 yards. He had reported insomnia one week prior to the first episode. He was instructed to stop driving and was withdrawn from the study when the investigator learned that he continued to drive. The insomnia, daytime drowsiness and sleep attacks were reported as completely resolved one week after discontinuation.

SP512DB/Subject 13704, a 44 year old male with a history of Parkinson's disease, sudden onset of sleep, dizziness, fatigue, drowsiness, depression, was taking rotigotine 4.5mg for one day in the de-escalation period of the study when he fell asleep while driving a heavy construction truck. The event lasted 1-2 seconds and was witnessed by two passengers. He continued in the study.

SP512OL/Subject 13703/83702, a 43 year old white female with a history of Parkinson's disease, constipation, Meniere's disease, borderline high blood pressure, Raynaud's syndrome, psoriasis, and other medical problems experienced sleep attacks 277 and then 366 days after starting open label rotigotine. The first episode occurred while driving, 10 minutes after patch application. She ran off the road without causing an accident. The narrative noted that she had not experienced sleep attacks prior to this event and that there was no indication of orthostatic hypotension or excessive daytime sleepiness. Approximately 90 days later, she experienced another sleep attack while driving. Her Epworth sleepiness scale sore had increased from 3 to 9 over the course of treatment. She continued in the trial.

SP512OL/Subject 12601/82601, a 65 year old female with a history of pedal edema, headaches, atypical chest pain, cholecystectomy, urinary tract infections, appendectomy, Parkinson's disease, and other medical problems had a sleep attack SAE. At the time of the event she was taking rotigotine 18mg/day and had been on this dose for 198 days. The event was described as sudden onset of sleep while driving that occurred without warning. She continued in the trial and the medication dose was unchanged. Concomitant medications at the time of the event included ibuprofen, tocopherol, aspirin, and pseudophedrine.

SP513OL/Subject 100502/800502 a 61 year old white male with Parkinson's disease, benign prostatic hypertrophy, obstructive pulmonary disease, nervousness, and excessive daytime sleepiness experienced a sleep attack 235 days after starting open label rotigotine. The subject had daytime sleepiness at baseline (Epworth score 11). His daytime sleepiness increased during the trial. The narrative reported that in 8/03 the subject experienced an episode of sudden onset of sleep but that the subject had warning prior to the event. Polysomnography in 10/03 showed high grade fragmentation of sleep probably in connection with the underlying Parkinson's disease. At this time the subject admitted to an episode of sudden onset of sleep without warning 3-4 weeks prior. The narrative provided no additional details about this event. The subject's rotigotine dose was reduced and he continued in the trial.

SP650 (Part II)/ Subject 14004/84003, a 55 year old white male with Parkinson's disease, depression, anxiety, panic attacks, hypercholesterolemia, sleep disturbance, and other medical problems experienced sleep attacks that began 77 days after starting open label rotigotine. Three attacks occurred over a five day period and the subject reported that they occurred without warning. One episode occurred while doing sit ups, one while watching television and the third while working on the computer. Concomitant medications at the time of onset of these events were carbidopa/levodopa, trazodone, paracetamol, amfebutamone, and lutein. Trial medication remained unchanged and the event was reported as resolved.

SP650 (Part I)/ Subject 14105/84105, a 59 year old white female with Parkinson's disease, osteoporosis, and other medical problems reported sleep attacks in a variety of situations since starting rotigotine 29 days prior. The attacks occurred daily, in the mid-afternoon, after replacing the trial medication patches in the morning. The narrative noted that the subject fell asleep at a traffic light. Following this event, the trial medication dosage was decreased and no further sleep attacks occurred. Concomitant medications at the onset of the SAE were carbidopa/leodopa, selegiline, trihexylphenidyl, minerals/vitamins, calcium, coenzyme Q, and alendronate.

Given the number of cardiac rhythm related SAEs, I reviewed these events more closely. I looked for SAEs suggestive of increased ectopy, ECG changes, or arrhythmia. Subject 14102, from study SP512 had an SAE of arrhythmia and the narrative described atrial fibrillation. Subject 14807 from study SP512 had an SAE of ECG abnormal and the narrative described ST wave changes associated with an MI. In the following paragraphs, I summarize information for other potentially important cardiovascular SAEs.

Palpitations

SP512/Subject 10408/80408, a 45 year old male with a history of depression, vesicocoele repair, Parkinson's disease, and other medical problems had an SAE of palpitations. At the time of the event his rotigotine dose was 13.5mg/day and he had been receiving that dose for 4 days. The palpitations were not associated with chest pain or any other symptoms. The subject admitted to palpitations in the past with exercise or high caffeine intake. A Holter monitor found a significant number of ventricular ectopics. The subject withdrew consent and the rotigotine dose was tapered and stopped. The palpitations stopped after rotigotine was withdrawn. The subject was evaluated by a cardiologist and underwent a repeat Holter and stress test. The second Holter showed a reduction in the number of ectopics. The stress test showed no evidence of ischemia, and multifocal ventricular ectopic beats at rest and exercise with no increase during exercise. Concomitant medications at the time of the event were aspirin, amantadine, selegiline, ascorbic acid, tocopherol, coenzyme Q10, and trazadone.

Arrhythmia ventricular

SP513(Part II)/Subject 105610/805609, a 67 year old female with a history of LBBB, stable angina, gastritis, GERD, diverticulosis, cystitis, Parkinson's disease, and other medical problems experienced a ventricular arrhythmia SAE. She was taking rotigotine 13.5mg/day at the time of the event and had been on that dosage for 106 days. She developed a ventricular arrhythmia (not specified) and was hospitalized. The subject reported palpitations. She was treated with magnesium and pyridoxine and the arrhythmia resolved. The subjects QTcB was 438msec at baseline and on treatment QTcBs ranged from 450-472msec. Concomitant medications at the time of the event were selegiline, herbal extracts, clorazepate, indapamide, bisoprolol, benazepril, nitrendipine, nicergoline, oxybutynin, and omeprazole. She continued in the trial and the trial medication was not changed.

Tachycardia ventricular

SP512OL/Subject 15303/85304, an 87 year old white male with Parkinson's disease, diabetes, benign prostatic hypertrophy, kidney stones, and an abdominal hernia, fainted 20 days after starting open label rotigotine. He was evaluated but not admitted and the narrative reported that labs and ECG did not show cardiac damage. He underwent an EP study which demonstrated inducible ventricular tachycardia and sinus node dysfunction. He underwent cardiac catherization and implantation of a cardioverter-defibrillator. Concomitant medications at the time of the SAE onset were tamsulosin, propranolol, glyburide, diphenoxylate, vitamin C and vitamin E. The subject continued in the trial.

N-0923-006-01/ Subject #2/JJH, a 70 year old male with Parkinson's disease, experienced ventricular ectopy and ventricular tachycardia during an iv study. On the first day of the study, the subject began iv infusion at 1μg/kg/hr and the infusion was increased to 8 μg/kg/hr over 2 hours. The dose was reduced to a maintenance dose of 2.8 μg/kg/hr. He continued on the maintenance dose for 6 hours but his tremors increased so the infusion was increased to 6μg/kg/hr over the next 9 hours. One hour and 45 minutes after reaching 6μg/kg/hr the patient began to have atrial and premature ventricular contractions which progressed to multifocal PVCs, couplets, and triplets. The infusion was decreased to 3μg/kg/hr. Over the next 2 hours, the ventricular arrhythmias decreased but the patient developed junctional rhythm and short episodes of ventricular tachycardia (10 beat, asymptomatic) and the infusion was stopped. No additional intervention was required. Within 90 minutes of infusion termination, the subject was in normal sinus rhythm. The narrative reported that the subject's baseline Holter monitor documented atrial flutter, and an insignificant amount of supraventricular or ventricular ectopic activity. Follow up Holter 5 days after discontinuation demonstrated premature atrial and ventricular beats that were clinically insignificant.