Comparison of Select AE Leading to Discontinuation Risks from Previous Safety Update and the Final Safety Update (pooled data), Early PD Trials.

AE leading to Discontinuation	Previous Safety Update Risk	Final Safety Update pooled Risk	RR
Hypokinesia	<0.1% (1/1093)	0.2% (2/1220)	2.0
Tremor	<0.1% (1/1093)	0.2% (2/1220)	2.0
Fall	<0.1% (1/1093)	0.2% (2/1220)	2.0
Dermatitis contact	<0.1% (1/1093)	0.2% (2/1220)	2.0
Hallucination	0.4% (4/1093)	0.7% (9/1220)	1.8
Myocardial infarction	0.2% (2/1093)	0.3% (4/1220)	1.5

Source NDA Safety Review pp.22-3, Final Safety Update, table 653.2.

When considering treatment duration at the time of discontinuation for AE, Schwarz found that the highest risk was within the first 6 months of treatment. Eleven percent (132/1220) of subjects discontinued for AEs within 0-6 months, 6% (40/654) within 6-12 months, 3% (17/550) within 12-18 months, 3% (12/489) within 18-24 months, 1% (6/453) for 24-30 months, 2% (7/367) for 30-36 months, 2% (5/220) at 36-42 months and 0/42 at >=42 months (Safety Update, p.36).

Cumulative Discontinuation for AE Risk for Advanced PD trials through the Final Safety Update Cutoff

Schwarz's presentation of AEs leading to discontinuation from advanced PD trials consisted of a table that provided the cumulative number of subjects that discontinued for a particular AE by dose at onset of the event. They did not provide an overall (all dose groups combined) rotigotine risk for each event. By totaling the number of subjects included in the listing 717.2.2, I determined that through the Final Safety Update cutoff 153 subjects (13.3%, 153/1151) discontinued from advanced PD trials for AEs. Through the previous safety update, the risk for discontinuation for AE from Phase II/III Advanced PD studies was 12.4% (73/589) (From NDA Review: numerator summed from data on pp.24-25, denominator from p. 119). After inclusion of new data the overall discontinuation for AE risk has increased only slightly.

Using table 717.2, I summed across dose groups to identify the AEs leading to discontinuation of at least 5 rotigotine subjects. The AEs leading to discontinuation of at least 5 rotigotine subjects were application site reactions (2.6%, 30/1151), nausea (1.8%, 21/1151), hallucinations (1.4%, 16/1151), vomiting (1.3%, 15/1151), dizziness (1.0%, 12/1151), Parkinson's aggravated (1.0%, 12/1151), somnolence (1.0%, 11/1151), dyskinesia (0.6%, 7/1151), myocardial infarction (0.5%, 6/1151), and confusion (0.4%, 5/1151).

In order to identify less frequently reported AEs leading to discontinuation of potential concern, I read through table 717.2 that listed all AEs leading to discontinuation reported for subjects in advanced PD trials in the Final Safety Update. Two subjects discontinued for QT increased and 1 subject discontinued for each of the following AEs: sleep attacks, hepatic enzymes increased, tachycardia, and bullous eruption. I provide details for these events in an appendix to this review. No advanced PD rotigotine subjects discontinued

for AEs of arrhythmia, rhabdomyolysis, hepatic failure, hepatic necrosis, pancreatitis, anemia, aplastic anemia, neutropenia, or toxic epidermal necrolysis.

Cumulative Discontinuation for AE Risk for RLS trials through the Final Safety Update Cutoff
Similar to the description above for the advanced PD trials, Schwarz's presentation of AEs leading to discontinuation from RLS trials consisted of a table that provided the cumulative number of subjects that discontinued for a particular AE by dose at onset of the event. By totaling the number of subjects included in the listing 817.2.2, I determined that through the Final Safety Update cutoff 84 subjects (20.8%, 84/404) discontinued from RLS trials for AEs. Through the previous safety update, the risk for discontinuation for AE from Phase II/III RLS studies was 6.9% (27/389) (From NDA Review: numerator summed from data on pp.25, 26; denominator from p. 119). For RLS trials through the final safety update, the discontinuation due to AE risk increased 3 fold compared to the previous safety update.

Using table 817.2, I summed across dose groups to identify the AEs leading to discontinuation of at least 5 rotigotine RLS subjects. The AEs leading to discontinuation of at least 5 rotigotine subjects were application site reaction (12.1%, 49/404), nausea (1.5%, 6/404), and insomnia (1.2%, 5/404).

In order to identify less frequently reported AEs leading to discontinuation of potential concern, I read through table 817.2.1 that listed all AEs leading to discontinuation reported for subjects in RLS trials in the Final Safety Update. One subject discontinued for QT increased 1 for arrhythmia, and 1 for hepatic enzymes increased. No RLS rotigotine subjects discontinued for AEs of rhabdomyolysis, hepatic failure, hepatic necrosis, pancreatitis, anemia, aplastic anemia, neutropenia, or toxic epidermal necrolysis. I summarize details for the subject who discontinued for hepatic enzymes increased and QT increased in an appendix to this review.

Discontinuations for AEs, Phase I Trials SP786 and SP787
No subjects discontinued from study SP786 for AEs. One subject discontinued from trial SP787 for an AE of syncope. This subject experienced orthostatic symptoms on assessments at 24 and 50 minutes after treatment with nasal spray rotigotine. The syncopal event occurred at the 24 minute assessment and was associated with an orthostatic decrease in diastolic blood pressure of 17mm Hg. The subject recovered after 10 minutes and discontinued from the trial.

2.8 Adverse Events

New AEs from Early PD trials
For the early PD subjects contributing new safety data to the Final Safety update, the AE risk was 86% (604/705). Schwarz provided a table summarizing AEs occurring in at least 5% of the subjects contributing new safety data in the Final Safety update. I provide information from that table below.

AEs Reported by at Least 5% of Rotigotine Treated Early PD Subjects Contributing New Safety Data in the Final Safety Update

Body System/Preferred Term	Rotigotine N=705 % (n)
Any Body System	86% (604)
Somnolence	21% (149)
Application Site Reaction	15% (107)
Nausea	13% (89)
Dizziness	12% (81)
Insomnia	11% (76)
Accident NOS	10% (72)
Fall	9% (62)
Back pain	8% (54)
Headache	8% (53)
Arthralgia	7% (47)
Constipation	6% (40)
Parkinsonism aggravated	5% (37)

Source: Table p.76 of Final Safety Update

In order to identify less frequently reported AEs of potential concern, I read through table 523.3 that listed all AEs for early PD subjects contributing new safety data to the Final Safety Update (pool S3 new). Thirty-four subjects (4.8%, 34/705) experienced hallucinations AEs, 11 subjects (1.6%, 11/705) experienced anemia AEs, 6 subjects (0.9%, 6/705) experienced sleep attack AEs, 4 subjects (0.6%, 4/705) experienced arrhythmia AEs, 1 subject (0.1%, 1/705) experienced a ventricular arrhythmia AE, 1 subject (0.1%, 1/705) experienced a QT increased AE, 1 subject (0.1%, 1/705) experienced a rhabdomyolysis AE. No early PD subjects contributing new safety data to the Final Safety Update experienced AEs of hepatic failure, hepatic necrosis, pancreatitis, aplastic anemia, neutropenia, or toxic epidermal necrolysis.

Early PD New and Previously Reported AE Data, Pooled

In the following table, I present the AEs occurring in at least 5% of the early PD trials subjects after pooling the new safety data with the safety data through the previous safety update.

AEs Reported by at Least 5% of Rotigotine Treated Early PD Subjects, Pooled Safety Data through the Final Safety Update

Body System/Preferred Term	Rotigotine N=1220 % (n)
Any Body System	91% (1109)
Application Site Reaction	39% (479)
Nausea	33% (399)
Somnolence	29% (355)
Dizziness	20% (247)
Insomnia	15% (183)
Headache	14% (175)

Vomiting	11% (135)
Accident NOS	10% (121)
Back pain	10% (121)
Upper Respiratory Tract Infection	9% (112)
Fall	9% (111)
Fatigue	8% (100)
Constipation	8% (95)
Arthralgia	7% (87)
Hypertension	6% (67)
Oedema peripheral	5% (63)
Anxiety	5% (63)
Urinary tract infection	5% (62)
Diarrhea	5% (62)

Source: Table p.75 of Final Safety Update

Since the majority of the new safety data for early PD subjects provided in the Final Safety Update are from open label trials, they do not lend themselves to comparative analyses that allow assessment of the causal relationship of AEs to rotigotine. To look for evidence of a causal relationship, I reexamined analyses of randomized controlled trial data from early PD trials as presented in the NDA review. For the events included in the above table, I present the AE risks from early PD randomized controlled trials for those instances where the risk among rotigotine subjects was at least 1.5 times greater when compared to placebo.

AE Risks for Select AEs from Early PD Randomized Controlled Trials

Body System/Preferred Term	Placebo N=289 % (n)	Rotigotine N=649 % (n)	RR
Vomiting	2.1% (6)	12.5% (81)	5.6
Application site reactions	13.8% (40)	36.8% (239)	2.7
Nausea	14.9% (43)	37.6% (244)	2.5
Insomnia	4.8% (14)	9.9% (64)	2.1
Urinary Tract Infection	1.4% (4)	2.8% (18)	2.0
Somnolence	15.6% (45)	24.8% (161)	1.6
Dizziness	11.1% (32)	18.2% (118)	1.6
Hypertension	2.1% (6)	3.1% (20)	1.5

Source NDA Review, pp. 35-36.

Cumulative AE Risk from Advanced PD trials through the Final Safety Update Cutoff
Schwarz provided a table that identified the AEs reported by at least 5% of advanced PD trial subjects through the Final Safety Update (cumulative). The AEs commonly reported by advanced PD subjects were generally similar to the AEs commonly reported by early PD subjects. Dyskinesia, hallucinations and Parkinson's aggravated appear in the table of AEs occurring in at least 5% of subjects for Advanced PD trials but not for early PD trials. I provide the AEs Reported by at Least 5% of Advanced PD Subjects in the table below.

AEs Reported by at Least 5% of Rotigotine Treated Advanced PD Subjects, Pooled Safety Data through the Final Safety Update

Body System/Preferred Term	Rotigotine N=1151 % (n)
Any Body System	80% (920)
Application Site Reaction	29% (329)
Somnolence	22% (248)
Nausea	21% (240)
Dizziness	14% (156)
Dyskinesia	12% (133)
Accident NOS	11% (131)
Fall	11% (123)
Insomnia	10% (118)
Upper Respiratory Tract Infection	9% (104)
Hallucinations	8% (95)
Back pain	8% (93)
Vomiting	8% (93)
Headache	8% (93)
Arthralgia	7% (82)
Parkinson's aggravated	6% (73)
Constipation	6% (65)

Source: Table p.128 of Final Safety Update

Cumulative AE Risk from RLS trials through the Final Safety Update Cutoff
Schwarz provided a table that identified the AEs reported by at least 5% rotigotine subjects from RLS trials through the safety update. I provide information from that table below.

AEs Reported by at Least 5% of Rotigotine Treated RLS Subjects, Pooled Safety Data through the Final Safety Update

Body System/Preferred Term	Rotigotine N=440 % (n)
Any Body System	87% (352)
Application Site Reaction	49% (198)
Influenza-like symptoms	17% (67)
Headache	15% (59)
Nausea	13% (70)
Fatigue	11% (46)
Back pain	10% (40)
Pruritis	8% (34)
Insomnia	8% (33)
Rash erythematous	8% (33)
Dizziness	6% (26)
Arthralgia	5% (20)
Hypertension	5% (20)

Source: Table p.146 of Final Safety Update

Despite the use of lower dosages in the RLS trials, the application site reaction risk (49%, 198/44) was notably higher than that reported in the early PD trials (39%, 479/1220) and advanced PD trials (29%, 329/1151). Somnolence, Falls, Accidents, and Hallucinations were not commonly reported in the RLS trials but were in the early PD and advanced PD trials.

AE Risks for Phase I Trials 786 and 787
Ten subjects reported 12 AEs in trial 786. All reported AEs were application site reactions with 5 subjects experiencing the reaction with the patch, and 5 subjects with nasal spray. The verbatim terms for the nasal spray reactions were nasal burning, nasal obstruction and prickling sensation (Final Safety Update, p.154). In trial 787, 12 subjects reported 50 AEs. The reported AEs were application site reactions (92%, 11/12), fatigue (42%, 5/12), dizziness (33%, 4/12), syncope (25%, 3/12), nausea (17%, 2/12), and sweating increased, asthenia, hot flashes, parasthesia, arthralgia, somnolence and rhinitis (reported by one subject each, 8.3%, 1/12) (Final Safety Update, p.155).

Other AEs of Special Focus
As they did in the NDA, Schwarz provided an analysis of select AEs of special focus. This group of special focus AEs included AEs pre specified in protocols, AEs previously described as being associated with the class of dopamine agonists, and other AEs identified by the sponsor. Many of these risks were included in the adverse events section above but are grouped together for this presentation. I provide a table summarizing these AEs below.

Special Focus AEs in Rotigotine Subjects from Pool S3 Studies through the Final Safety Update

Body System/Preferred Term	Rotigotine N=1220 % (n)
Class Effect AEs	
Nausea	33% (399)
Somnolence	29% (355)
Insomnia	15% (183)
Extremity edema	14% (166)
Vomiting	11% (135)
Psychotiform reaction	7% (89)
Suspected orthostatic hypotension	7% (86)
Dyskinesia	5% (59)
Vision abnormal	3% (36)
Convulsions	<1% (1)
Neuroleptic malignant syndrome*	<1% (1)
Other AEs	
Musculoskeletal pain	23% (279)
Headache	14% (175)
Fall	9% (111)

Hypertension	6% (74)
Abdominal pain	4% (45)
Syncope	3% (33)
Special Interest AEs	
Severe site reaction	2% (28)
Sleep attacks	2% (19)
Severe cardiac arrhythmia	<1% (3)

* Verbatim term: rhabdomyolysis.
Source: table in Final Safety Update, p.103.

2.9 FDA Discussion
Schwarz provided their Final Safety Update as part of their response to issues raised in the Approvable letter for rotigotine. The Final Safety Update includes data for 706 newly exposed subjects in phase II/III trials, with the majority of these new subjects exposed in advanced PD trials. The Final Safety Update also includes data for subjects exposed in phase I trials and for subjects that appeared in previous submissions but that are receiving ongoing rotigotine treatment in open label trials.

The Final Safety Update includes 24 new rotigotine deaths and all but one of these new deaths occurred in subjects participating in open label trials. All 29 rotigotine deaths in the development program (cumulative) have occurred in PD treated subjects (early PD n=13, advanced PD n=16, no deaths in RLS subjects). The reported causes of death appeared to be the types of causes expected in the treated populations.

In the Final Safety Update Schwarz reported SAEs, discontinuation for AEs and all AEs for the treated populations through the 10/31/05 cutoff date. In most cases, addition of the new safety data resulted in minimal changes in specific adverse event risks when compared to previous submissions.

2.10 Conclusions
The sponsor's Final Safety Update did not identify any new safety related concerns with rotigotine and did not lead to any changes to rotigotine's safety profile as described in the previous submissions.

3.0 CARDIAC ARRHYTHMIA ADVERSE EVENTS

3.1 Background

The rotigotine NDA included reports of cardiac arrhythmias in rotigotine exposed subjects but it was not clear if these events were related to rotigotine or merely represented "background" events in the treated study subjects. Dr. Racoosin discussed these arrhythmia events in her supervisory memo dated 2/28/06. Specifically Dr. Racoosin highlighted the cases of arrhythmia in clinical pharmacology studies as well as sudden deaths (1 witnessed, 2 not witnessed) that could possibly have been due to arrhythmia. In the approvable letter, the Division requested additional analyses of

cardiovascular safety data in order to examine if rotigotine may be associated with an increased risk of cardiac arrhythmia AEs. Specifically, the Division requested a comprehensive analysis of treatment emergent cardiac arrhythmia AEs based on a treatment-blinded cardiologist re-coding of events from completed phase II and III trials in early stage PD, advanced PD, and restless legs syndrome. In the response to the approvable letter, Schwartz included the requested analysis of cardiac arrhythmia AEs.

3.2 Methods

Schwarz analyzed all treatment emergent cardiac arrhythmia AEs from double blind placebo controlled trials and explained how they classified events with respect to dose. Schwarz defined "treatment emergent" as having an onset after initiation of trial drug administration, including 1 day after patch removal and during the 30 day safety follow up period. As was done in their NDA presentations, rotigotine dose was classified as the dose at onset of the event and for events occurring on dose switch days, dose was assigned to the lower rotigotine dose administered. Events occurring during medication gaps were attributed to drug with "no dose" recorded. Patients could have had events at more than one dose and when this occurred, the events were assigned to the lowest dose at which the event occurred (dose groups not mutually exclusive with respect to individual subjects). For subjects randomized to rotigotine but receiving a placebo patch at the time of the event (during placebo run in periods), the events are included in the placebo columns. Schwarz provided a separate analysis that assigned events to the rotigotine dose of longest duration for the subject who experienced the event.

Schwarz re-coded cardiac arrhythmia events using the MedDRA dictionary version 8.1. For the included controlled trials Schwarz physicians identified all AEs that had been coded to the following terms:

Higher Level Group Terms (HLGTs) included:
- Cardiac arrhythmias (Primary system organ class [SOC] Cardiac disorders)
- Cardiac disorders signs and symptoms (Primary SOC Cardiac disorders)

High level terms (HLTs) terms included:
- Electrocardiogram (ECG) investigations (Primary SOC Investigations)
- Heart rate and pulse investigations (Primary SOC Investigations)

Preferred terms included:
- Cardiac death (Primary SOC General disorders and administration site conditions)
- Sudden cardiac death (Primary SOC General disorders and administration site conditions)
- Sudden death (Primary SOC General disorders and administration site conditions)

Schwarz did not include the AE terms "cyanosis" or "ECG signs of myocardial ischemia" in their analysis.

Schwarz limited their analysis of cardiac arrhythmia AEs from uncontrolled trials to SAEs or AEs that led to trial discontinuation (as agreed upon with the Division prior to the submission).

After identifying subjects with an event coded to one of the pre-specified MedDRA search terms, Schwarz wrote narratives for these events. These event narratives were then blinded with regards to treatment. The narratives and any pertinent supporting material (ex. ECGs) were forwarded to a consultant cardiologist from — for review. The consultant cardiologist reviewed the submitted material and then re-coded the AEs. In the event that the consultant cardiologist felt that the available information was insufficient to allow recoding of the event, the original coding was used. Schwarz presented tables using the original coding and the new coding results. (Arrhythmia analysis Report, p.16).

Schwarz provided summary tables with different analyses of the arrhythmia data. As noted above, Schwarz summarized AE risks resulting from the original AE coding and also for the re-coding based on the consultant cardiologist analysis. Schwarz also provided different tables that compared AE risks (# events/#subjects), AE risks by rotigotine dose (dose for longest treatment duration and dose at onset), AE rates (# events/ person months of exposure), and AE cumulative risks from survival analyses. In addition, Schwarz presented arrhythmia risks for various data groupings by indication including all Parkinson's disease plus Restless Leg Syndrome, all Parkinson's disease alone, early Parkinson's disease alone, advanced Parkinson's disease alone, and Restless Leg Syndrome alone. Lastly, Schwarz made different presentations based on the study design. Schwarz presented data from double blind placebo controlled studies alone, open label studies (excluding extensions) alone, and for all studies (controlled and uncontrolled trials) combined.

The following table identifies the studies that contributed data to the arrhythmia analyses.

Rotigotine Trials Included in the Analysis for Arrhythmias

Phase	Type	Trials
Early Parkinson's Disease Trials		
1	Uncontrolled	SP630, SP788, SP651
2a	Placebo controlled	SP534 part I, SP 534 part II, SP535
	Uncontrolled	SP540
2b	Placebo controlled	SP506
3	Placebo controlled	SP 512 part I
	Placebo and active controlled	SP513 part I
	Uncontrolled	SP512 part II, SP 513 part II
3b	Active controlled	SP825
	Uncontrolled	SP824, SP826, SP833
Advanced Parkinson's Disease Trials		
2a	Uncontrolled	SP533, SP591
2b	Placebo controlled	SP511
3	Placebo controlled	SP650 part I
	Placebo and active controlled	SP515
	Uncontrolled	SP650 part II, SP516
3b	Uncontrolled	SP824, SP826, SP833
RLS Trials		
1	Uncontrolled	SP628

2a	Placebo controlled	SP666
2b	Placebo controlled	SP709
	Uncontrolled	SP710

From Cardiac Arrhythmia review submission, pp. 19, 20, and 21

3.3 Results

Original Coding
Since the purpose of this report was to present a re-analysis of arrhythmia AEs after these events had been re-reviewed and re-coded, the AE risks based on the original coding will not be reviewed.

Blinded Re-coding
Assessment of the outcome of the Re-coding process
Schwarz provided a table that summarized the percentage of preferred terms that were changed by the cardiologist that reviewed and recoded arrhythmia AEs (P.116). I provide that table below.

Number of treatment-emergent cardiac arrhythmia related AE preferred terms that changed based on recoding by the blinded Cardiologist

Number of events per treatment group	Placebo	Rotigotine	Ropinirole	Pramipexole	Total
	100	212	30	27	369
Preferred term not changed, % (n)	74% (74)	74% (157)	97% (29)	89% (24)	77% (284)
Preferred term changed[a], n (%)	26% (26)	26% (55)	3% (1)	11% (3)	23% (85)
Preferred term deleted[b], n (%)	16% (16)	12% (25)	3% (1)	7% (2)	12% (44)

Note: "Changed" or "deleted" is based on recoding by the blinded Cardiologist.
a. Preferred term "changed" also includes preferred terms "deleted."
b. Deleted=not considered an AE by the blinded Cardiologist.

The number of preferred terms changed by the recoding process was relatively small. A higher percentage of preferred terms were changed for the rotigotine and placebo groups compared to the other treatment groups. I include as an appendix to this review (appendix 5.4) a table that lists all of the arrhythmia AE terms that were changed by the consultant cardiologist.

Double Blind Placebo Controlled Trials
Following the re-coding of adverse event terms, there was little difference in overall arrhythmia event risk when comparing the treatment groups for the pooled randomized controlled trials. For the Parkinson's disease plus Restless leg syndrome data pool, the arrhythmia risk for the rotigotine treated subjects was 5% (78/1669) compared to 6% (41/681) for placebo subjects, 4% (10/228) for ropinirole subjects and 6% (12/202) for pramipexole subjects. The following table summarizes the results for other data pools.

Arrhythmia Adverse Event Risk by Treatment for Select Data Pools of Randomized Controlled Trial Data

Data Pool	Placebo	Rotigotine	Ropinirole	Pramipexole
All Parkinson's disease	6% (37/612)	5% (66/1335)	4% (10/228)	6% (12/202)
Early Parkinson's disease	6% (18/295)	5% (32/677)	4% (10/228)	NA
Advanced Parkinson's disease	6% (19/317)	5% (34/658)	NA	6% (12/202)
RLS	6% (4/69)	4% (12/334)	NA	NA

Source: Table, Arrhythmia analysis report, p.44

Schwarz provided tables that listed the specific arrhythmia AEs for each of the data pools included in the above table. I reviewed these tables to identify if there were any specific arrhythmia events occurring in at least 2 rotigotine subjects and where the risk was elevated at least 1.5 fold among rotigotine subjects compared to subjects receiving placebo. Those events are provided in the following table.

Specific Arrhythmia Adverse Event Risks by Treatment for Select Data Pools of Randomized Controlled Trial Data

Adverse Event	Rotigotine	Placebo	RR
All Parkinson's Disease plus Restless Leg Syndrome			
Palpitations	1.1% (18/1669)	0.7% (5/681)	1.6
Atrial Flutter	0.1% (2/1669)	0/681	
Sinus Tachycardia	0.1% (2/1669)	0/681	
Electrocardiogram ST segment depression	0.1% (2/1669)	0/681	
Electrocardiogram ST segment abnormal	0.1% (2/1669)	0/681	
All Parkinson's Disease			
Palpitations	1.2% (1335)	0.7% (4/612)	1.7
Atrial Flutter	0.1% (2/1335)	0/612	
Sinus tachycardia	0.1% (2/1335)	0/612	
Electrocardiogram T wave abnormal	0.1% (2/1335)	0/612	
Early Parkinson's Disease			
Palpitations	1.2% (8/677)	0.7% (2/295)	1.7
Bundle Branch Left	0.3% (2/677)	0/295	
Tachycardia	0.7% (5/677)	0.3% (1/295)	2.3
Electrocardiogram QT corrected interval prolonged	0.4% (3/677)	0/295	
Electrocardiogram T wave abnormal	0.3% (2/677)	0/295	
Advanced Parkinson's Disease			
Palpitations	1.2% (8/658)	0.6% (2/317)	2.0
QRS axis abnormal	0.5% (3/658)	0.3% (1/317)	1.7
Restless Leg Syndrome			

Tachycardia	0.9% (3/334)	0/69	
Electrocardiogram QT corrected interval prolonged	0.6% (2/334)	0/69	
Electrocardiogram ST-T segment abnormal	0.6% (2/334)	0/69	

Source: Arrhythmia analysis report, Tables 1d.1.1a, 1d.1.2a, 1d.1.3a, 1d.1.4a, and 1d.1.5a

In general the risks for specific arrhythmia events were low and similar when comparing the rotigotine and placebo treatment groups. The risk for palpitations was elevated among rotigotine subjects compared to placebo subjects in all of the Parkinson's disease trials safety data pools but not in the RLS data pool.

Schwarz provided two separate dose response analyses, one where the event was classified by the dose that the subject took for the longest duration and one where the event was classified by the dose at the onset of the event. Since there were generally few arrhythmia events, the dose response analyses were not robust (too few events to allow for reliable analyses). For the most commonly reported event, palpitations, neither dose response analysis appeared to suggest a dose response relationship.

Due to the similarity in duration of exposure per subject in the rotigotine and placebo treatment groups, calculation of arrhythmia event rates (# events/patient months exposure) did not lead to any meaningful differences for the relative risks of arrhythmia events when compared to previous analyses that were based on number of exposed subjects (Source Table 1d.4.1a).

As noted above, Schwarz provided arrhythmia AE cumulative rates based on survival analyses for the data pools. This analysis did not lead to meaningful differences in results when comparing AE risks in the controlled trials. I provide the results for the all Parkinson's disease plus Restless leg syndrome population below.

Cardiac Arrhythmia AE Cumulative Rates from Survival Analyses for the All Parkinson's Disease plus RLS Data Pool

Parameter	Placebo	Rotigotine	Ropinirole	Pramipexole
Subjects at risk	681	1669	228	202
Subjects with an arrhythmia AE	41	78	10	12
Crude rate (%)	6.02	4.67	4.39	5.94
Cumulative rate (%)	7.69	6.25	4.86	6.19

Cumulative Rate= 1 minus the product limit estimate of the survival rate at the end of the interval. Intervals were every 2 weeks through week 8, then every 4 weeks through week 16 then every 8 weeks through week 40.

For each of the remaining safety data pools (all Parkinson's disease alone, early Parkinson's disease, advanced Parkinson's disease, and Restless leg syndrome alone) the cumulative rate for arrhythmia events was greater in the placebo group than in the rotigotine group for the entire duration as well as for each interval (Source Tables 1d.5.2, 1d.5.3, 1d.5.4, and 1d.5.5).

at particular dosages and the relatively small number of events are limitations of the dose response analyses.

The AE "palpitations" was the only arrhythmia AE reported for at least 1% of subjects (1%, 29/2775). The other AEs reported by at least 10 subjects were tachycardia (n=24), atrial fibrillation (n=20), AV block first degree (n=17), electrocardiogram QT corrected interval prolonged (n=16), and ventricular extrasystoles (n=11).

In addition to the arrhythmia AEs noted above, other AEs of interest include AV block second degree which was reported for one subject, and complete heart block was reported for one subject. Three subjects had AEs of ventricular tachycardia, one had an AE of ventricular arrhythmia and no subjects had events of ventricular fibrillation, cardiac arrest, or asystole (Source: Table 1d.1.1c).

3.4 Schwarz discussion

The sponsor felt that their analyses demonstrated that cardiac arrhythmia AE risks were not significantly different when comparing the rotigotine treated group to the placebo and active control groups. Schwarz felt that the analyses demonstrated no new safety signals in terms of cardiac arrhythmias. Schwarz also commented that new Holter monitoring studies are not necessary.

3.5 FDA Narrative review

The sponsor provided narratives for the AEs included in the analyses. I read the list of all cardiac arrhythmia AEs and selected a subset of these narratives for review. I selected narratives for events of interest identified in the NDA review (ex. QT prolongation), for events of particular severity (ex. Ventricular tachycardia), and events where the diagnosis was not clear from the coded preferred term (ex. Arrhythmia, ventricular arrhythmia).

Electrocardiogram QT corrected interval prolonged

I identified 16 subjects with prolonged QTc interval AEs that were either randomized to rotigotine or received rotigotine in uncontrolled trials. One subject randomized to rotigotine (SP709/11607) actually experienced the event prior to receiving study drug and withdrew and a second subject (SP511/1024) experienced the event while receiving placebo. These two events are not considered further. For the remaining 14 rotigotine subjects that experienced a prolonged QTc interval AE, I summarized in the following table select details from the submitted narratives.

Subject	Sex/Age	Indication	BL QTc	Max QTc	Tx duration	Dose	Outcome
SP506/1355	71/M	PD, early	357-415	446	16 days	13.5mg	D/C, F/U QTc 415
SP506/1457	52/F	PD, early	416-427	470	29 days	18mg	D/C, F/U QTc 478
SP506/1563	61/M	PD, early	380-421	455	78 days	13.5mg	Finished, F/U QTc 425
SP506/1728	67/M	PD, early	374-448	442	Visit 2	N/A	No other QTc>430
SP512/13104	48/F	PD, early	459	451	1 month	4.5mg	Next QTc 439

SP512/14102	68/M	PD, early	396-406	545	6 months	13.5mg	D/C, no F/U ECG
SP512OL/13004	64/M	PD, early	N/A	N/A	N/A	4.5mg	D/C, resolved
SP513/103606	50/F	PD, early	398	410	27 months	18mg	D/C, resolved
SP513/104404	50/M	PD, early	400	480	2 months	18mg	Continued, resolved
SP516/102805	71/M	PD, advanced	462	531	N/A	27mg	Dose decreased, not resolved
SP650DB/10514	77/M	PD, advanced	431-459	548	7 days	18mg	Resolved, no other QTc>475
SP650DB/13905	84/M	PD, advanced	428	516	5 months	13.5mg	D/C, F/U QTc 441
SP666/10604*	60/M	RLS	410	532	7 days	2.25mg	Ongoing
SP709/10423	63/M	RLS	446-455	501	7 days	4.5mg	D/C, resolved

*ECG results were not included in the Response submission and were requested by the Division. The sponsor provided these results in an email dated 12/4/06. The QT interval was provided and the QTc was calculated by the reviewer using the included data.

These cases add little new information about rotigotine's effect on the QT interval. The NDA included the most relevant information on this topic. Dr. Stone felt that the NDA ECG data did not suggest an effect of rotigotine on cardiac repolarization although he acknowledged the limitations of these data. The identified cases included some with relatively small increases in QTc, some that resolved on drug, and others of unknown significance.

Arrhythmia

Four subjects had AEs that were coded to the preferred term arrhythmia. The narratives included insufficient details to allow for classification of these arrhythmias. For the first case, the event occurred during the baseline phase, prior to rotigotine administration. For the second case, the AE occurred during the follow up phase, after rotigotine was discontinued. For the third case, study drug was continued and the event did not recur. The fourth case occurred in a subject with a history of arrhythmia. I summarize details from these cases below.

Subject SP709/11801 This 74 year old subject with RLS experienced an AE of arrhythmia during the baseline (pre study drug) period of a trial.

Subject SP512OL/12203 This 76 year old male with PD, hypertension, and erectile dysfunction experienced an arrhythmia, worsening coronary artery disease and a syncopal episode during the follow-up period, after study drug had been stopped. The narrative did not describe the arrhythmia and stated that no ECG was recorded on the day of these events.

Subject SP511/1608 This 73 year old male with advanced PD was had been treated with rotigotine for about a month and was receiving 18mg/day when he developed an arrhythmia that was not described. The narrative noted that no therapeutic measures were used to treat the event and the outcome was reported as recovered. The subject continued in the study. The narrative included the subjects ECG data. The subject had baseline QTc (Bazett) results of 487 and 486msec. His reported QTc results closest to the time of the event were 474, 474, 470, and 461msec. The subject had 1 on-drug QTc>500msec (actual QTc 512msec) that was recorded approximately 2 weeks prior to the arrhythmia AE. The subject's QTc results subsequent to the 512msec result and prior to the arrhythmia were all <=465msec.

Subject SP710/12207 This 62 year old female with RLS and a history of cardiac arrhythmia, hypertension, and thyroid carcinoma experienced an AE of arrhythmia that was not classified. The arrhythmia ("rhythm

disturbances") occurred at night and with physical strain. No ECG was recorded on the day of the event and no therapeutic measures were used to treat the arrhythmia. She was evaluated by a cardiologist and an ECG at that visit did not capture an arrhythmia. The subject withdrew from the trial for this event.

Ventricular Tachycardia

Subject SP512OL/15303 This 87 year old male with PD, diabetes, BPH, kidney stones, and abdominal hernia experienced a syncopal event and was taken to a hospital. He was evaluated (labs, ECG) and no evidence of cardiac damage was found and he was sent home. He underwent follow up EP testing which found inducible ventricular tachycardia and sinus node dysfunction. His diagnoses were ventricular tachycardia and sick sinus syndrome. He underwent implantation of a cardioverter/defibrillator and he continued in the trial. Concomitant medications were tamsulosin, propranolol, glyburide, vitamin C and E.

Subject SP709/10404 This 63 year old female with RLS, hypothyroidism, and remote history of tobacco use experienced 3 episodes of ventricular tachycardia over a 3 day period (lasting an average of 30 minutes each). These events occurred after 15 days of rotigotine treatment and were described as non-serious. The narrative did not state if these episodes were associated with symptoms or how these events were captured. The narrative included the subject's study ECG results and all were read as normal with the exception of the last ECG (isolated ventricular beat) which was recorded almost 2 months after these events occurred. The subject continued in the trial.

Subject SP650/12003 This 80 year old male with a history of ventricular tachycardia, paroxysmal atrial fibrillation, erectile dysfunction, depression, confusion, benign prostatic hypertrophy, and inguinal hernias, had an AE of ventricular tachycardia during open label treatment with rotigotine (18mg/day). In a preceding RCT where this subject received placebo, he had an AE of atrial fibrillation. The baseline ECG from the open label trial showed atrial fibrillation while the subsequent ECGs were read as demonstrating first degree AV block with ST-T wave changes. No ECG was captured on the day of the ventricular tachycardia event. The narrative reported that the event was a nonserious AE, that no therapeutic measures were administered to treat the ventricular tachycardia, and that the event outcome was not resolved. Concomitant medications were digoxin, levofloxacin, pantoprazole, potassium, and carbidopa/levodopa.

*This narrative was provided in an email dated 12/6/06. The email was a response to a Division request for information.

Ventricular Arrhythmia

SP513OL/105610 This 66 year old female with PD, gastritis, reflux, LBBB, and hypertension had been taking rotigotine 13.5mg/day for 105 days when she experienced a ventricular arrhythmia (not further classified). The narrative did not explain how the event was captured or if the event was associated with symptoms. The event was considered serious. No therapeutic measures were administered and the event was considered resolved.

Syncope

The sponsor's analyses summarized AEs re-coded to cardiac arrhythmia preferred terms but excluded one potentially important event that could be a manifestation of arrhythmia, namely syncope. For the original coding used in the NDA, in early PD controlled trials, syncope occurred in 1.1% (7/649) of rotigotine subjects and 0.7% (2/289) placebo subjects (NDA Safety review, p.35). In study SP650DB, an advanced PD RCT, no rotigotine subjects (0/229) and 1 placebo subject (0.8%, 1/120) experienced an AE of syncope (120 day SU, table 36.2.1). In the RLS phase I and II controlled trials (SP628, SP666, and SP709) syncope was reported by no rotigotine subjects (0/358) and 1.4% (1/69) of placebo subjects (Final Safety Update Table 813.1). These data do not suggest an increased risk for syncope among rotigotine treated subjects.

3.6 FDA discussion

The rotigotine NDA included cardiac arrhythmia adverse events but the relationship between these events and rotigotine was not clear. Individual events may signal potential safety problems but are insufficient in most cases for proving causal relationships.

Therefore, the Division requested a reanalysis of adverse event data, to look for evidence of increased cardiac arrhythmia risk in rotigotine treated subjects compared to placebo or active comparator treated subjects.

The sponsor submitted their reanalysis of arrhythmia related AEs and did not find strong evidence of an increased arrhythmia risk with rotigotine. With the exception of palpitations, most of the examined arrhythmia AEs risks were similar among the different treatment groups. The significance of the slightly increased risk of palpitations with rotigotine is uncertain given that palpitations are not a specific symptom of a cardiac arrhythmia. A review of previously submitted data did not suggest an increased risk of syncope when comparing risks for rotigotine and placebo treated subjects. The data do not support the need for a study of rotigotine exposed subjects using Holter monitoring.

In a response to the Division's inquiry, Schwarz stated in a 4/11/07 email that they would be submitting the results from their QT study (SP864) in [redacted]

4.0 COMPULSIVE BEHAVIOR ADVERSE EVENTS

4.1 Background

There are reports of compulsive gambling, compulsive sexual behavior, compulsive shopping and compulsive eating in patients treated with many of the approved Parkinson's disease medications. Assessment of the relationship between these behaviors and treatments has been hampered by the lack of adequate data. Data from development programs for previously approved Parkinson's disease treatments are inadequate because the programs did not actively collect risk data for these behaviors and spontaneous reports provide limited information due to incomplete capture of events (underreporting, inadequately described events etc.) lack of precise exposure estimates, and lack of available background risk data, particularly in the population of interest.

In their NDA, Schwarz did not address compulsive behavior AEs reported for rotigotine treated subjects in their development program trials. The Division requested that Schwarz identify AEs of compulsive gambling, hypersexuality, compulsive eating or any other compulsive behaviors in rotigotine treated study subjects. In addition to identifying the events, the Division requested that Schwarz provide narratives that include information about these events. Schwarz provided this information in their response to the approvable letter.

4.2 Methods

Schwarz physicians searched for the following MedDRA terms to identify compulsive behaviors: pathological gambling, gambling, obsessive-compulsive personality disorder, obsessive thoughts, obsessive-compulsive disorder, impulse control disorder, hyperphagia, eating disorder, appetite disorder, sexual activity increased, libido increased (Compulsive Behavior Review, p.5). Schwarz presented these events in their report using preferred terms from the modified WHO-ART dictionary to assure consistency with the NDA presentations (NDA presentations used WHO-ART).

Schwarz analyzed data from phase 1, 2, and 3 rotigotine trials. The table below summarizes the trials that were included in the analysis.

Rotigotine Trials Included in the Analysis for Compulsive Behaviors

Phase	Type	Trials
Early Parkinson's Disease Trials		
1	Uncontrolled	SP630, SP788, SP651
2a	Placebo controlled	SP534 part I, SP 534 part II, SP535
	Uncontrolled	SP540
2b	Placebo controlled	SP506
3	Placebo controlled	SP 512 part I
	Placebo and active controlled	SP513 part I
	Uncontrolled	SP512 part II, SP 513 part II
3b	Active controlled	SP825
	Uncontrolled	SP824, SP826, SP833
Advanced Parkinson's Disease Trials		
2a	Uncontrolled	SP533, SP591
2b	Placebo controlled	SP511
3	Placebo controlled	SP650 part I
	Placebo and active controlled	SP515
	Uncontrolled	SP650 part II, SP516
3b	Uncontrolled	SP824, SP826, SP833
RLS Trials		
1	Uncontrolled	SP628
2a	Placebo controlled	SP666
2b	Placebo controlled	SP709
	Uncontrolled	SP710

Source Compulsive Behaviors Report, pp. 6-7.

4.3 Results

Overall

Schwarz identified 31 study subjects from the rotigotine development program with one or more AEs coded to the MedDRA terms suggestive for compulsive behavior. The breakdown by treatment included 29 rotigotine subjects (1%, 29/2775), 2 pramipexole subjects and 1 ropinirole subject. Summing the number of subjects by treatment does not equal 31 because one subject experienced compulsive behavior AEs on pramipexole and again subsequently on rotigotine. When analyzed by indication, 15 rotigotine subjects from early PD trials (1.2%, 15/1220) and 14 subjects from advanced PD trials (1.2%, 14/1151) experienced one or more compulsive behavior AEs. No subjects from RLS studies (rotigotine n=404) experienced compulsive behaviors. Among rotigotine treated subjects, the ratio of males to females that experienced compulsive behaviors (1.9) was similar to the ratio of males to females in the early PD (1.6) and advanced PD (1.8) study populations (Final Safety update, p.44, p.120). Gambling was the compulsive event most frequently reported (n=15) followed by increased libido/hypersexuality (n=11).

The following table identifies the rotigotine subjects that experienced compulsive behaviors and provides information about these events.

Subject (age, sex)	Dose at onset (days on treatment)	Reported Term	WHO-ART term	Action taken/ Outcome
SP512/11601 (55/female)	27mg (1046)	Compulsive eating	Neurosis	Dose unchanged/ not yet recovered
SP512/11704 (44/male)	18mg (902)	Compulsive gambling	Neurosis	Dose unchanged/ Recovered
SP512/12007 (58/male)	18mg (482)	Compulsive gambling disorder	Neurosis	Dose reduced/ Recovered
SP512/13501 (33/female)	13.5mg (890)	Impulsive control disorder (gambling)	Neurosis	Dose reduced/ Recovered
SP512/13505 (50/male)	4.5mg (1)	(Gambling) Impulsive control disorder	Neurosis	Dose unchanged/ Not available
SP512/14707 (59/female)	22.5mg (492)	Increased urge to gamble	Neurosis	Dose reduced/ Recovered
SP513/108011 (64/male)	— (507)	Gambling (compulsive behavior)	Neurosis	Dose unchanged/ not yet recovered
SP515/113406 (59/male)	9mg (1)	Gambling	Neurosis	Dose unchanged/ not yet recovered
SP650/10102 (50/male)	13.5mg (418)	Compulsive disorder (gambling)	Neurosis	Drug discontinued /Not yet recovered
SP650/13209 (40/female)	13.5mg (13)	Compulsive gambling	Neurosis	Dose unchanged/ Recovered
SP833/14712* (53/female)	18mg (79)	Increased compulsive behavior	Neurosis	Drug discontinued /Recovered
SP515/100306 (50/male)	18mg (80) 18mg (80) 18mg (204)	Gambling addiction Polyphagia Hypersexuality	Neurosis Appetite increased Libido increased	Dose unchanged/ not yet recovered
SP650/12909 (61/male)	27mg (336) 27mg (306)	Hypersexuality Punding	Libido increased Neurosis	Drug discontinued /Recovered Drug discontinued /Not yet recovered
SP512/11202 (49/male)	22.5mg (814)	Hypersexuality	Libido increased	Dose unchanged/ Not available
SP513/101606 (47/female)	27mg (716)	Hypersexuality	Libido increased	Dose reduced/ Recovered
SP513/107101 (63/male)	— ıg (960)	Hypersexuality	Libido increased	

SP515/107910 (51/male)	9mg (1)	Increased sex drive	Libido increased	Dose unchanged/ not yet recovered
SP515/107912 (59/male)	9mg (1)	Increased sex drive	Libido increased	Dose unchanged/ not yet recovered
SP515/108803 (67/female)	— (39)	Hypersexuality	Libido increased	Dose unchanged/ Recovered
SP516/103503 (79/male)	13.5mg (10)	Hypersexuality	Libido increased	Dose unchanged/ Recovered
SP515/100307 (57/female)	18mg (80)	Polyphagia	Appetite increased	Dose unchanged/ Not available
SP824/14712* (53/female)	18mg (79)	Increased compulsive behavior	Neurosis	Drug discontinued /Recovered
SP630/80202 (67/male)	— 420)	Compulsive gambling	Neurosis	Dose unchanged/ Not available
SP630/80305 (46/female)	22.5mg (332)	Gambling compulsion	Neurosis	Drug discontinued /Lost to follow up
SP824/14714 (52/female)	4.5mg (7)	Impulse control disorder-increasing (pathological gambling)	Personality disorder	Dose unchanged/ Recovered
SP512/13707 (53/male)	4.5mg (1)	Compulsive disorder Pathological gambling	Neurosis Neurosis	Dose unchanged/ Not yet recovered Drug discontinued /Not yet recovered
SP515/100301 (58/male)	18mg (85)	Gambling addiction	Neurosis	Dose unchanged/ Not yet recovered
SP650/12105 (71/male)	27mg (57)	Compulsive behavior	Neurosis	Dose unchanged/ Recovered
SP515/109103 (66/male)	18mg (50)	Increased libido	Libido increased	Dose unchanged/ Not yet recovered
SP512/14606 (59/male)	13.5mg (19)	Increased libido	Libido increased	Dose unchanged/ ongoing

Source: Table from Compulsive Behavior Report, pp.15-16.
* This subject experienced a compulsive behavior in two separate trials

Parkinson's disease Placebo Controlled Trials
Considering the subset of pooled data from the Parkinson's disease controlled trials, the risk for compulsive behavior was <1% (5/1335) for rotigotine subjects and was zero (0/612) for placebo subjects. The following table summarizes compulsive behavior risk from rotigotine Parkinson's disease controlled trials.

Indication	Placebo % (n/N)	Rotigotine % (n/N)	Ropinirole % (n/N)	Pramipexole % (n/N)
All PD	(0/612)	<1% (5/1335)	(0/228)	1% (2/202)
Early PD	(0/295)	<1% (2/677)	(0/228)	NA
Advanced PD	(0/317)	<1% (3/658)	NA	1% (2/202)

Source: Table from Compulsive Behavior Report, p.9

The preferred terms for the compulsive behaviors experienced by rotigotine subjects from the early PD trials were libido increased and neurosis (verbatim term pathological gambling). The preferred terms for the compulsive behaviors experienced by rotigotine subjects from the advanced PD trials were libido increased and neurosis (n=2, verbatim terms gambling addiction, compulsive behavior[3]). One rotigotine subject discontinued and the remaining 4 subjects continued in the trial without changes in their rotigotine doses. For 4 rotigotine subjects the event was ongoing at the time of the data cutoff. The pramipexole subjects experienced libido increased and neurosis (verbatim term obsessions).

Parkinson's disease Open Label Trials (non extension)
The following table summarizes compulsive behavior risk from rotigotine Parkinson's disease open label (non-extension) studies.

Indication	Rotigotine % (n/N)	Ropinirole % (n/N)
All PD	1% (4/376)	4% (1/26)
Early PD	1% (3/207)	4%(1/26)
Advanced PD	<1% (1/169)	NA

Source: Table from Compulsive Behavior Report, p.11

The preferred terms for the compulsive behaviors experienced by rotigotine subjects from the early PD trials were neurosis (n=2, verbatim term pathological gambling) and personality disorder (verbatim term impulse control disorder-pathological gambling). The preferred term for the compulsive behavior experienced by the rotigotine subject from the advanced PD trials was neurosis (verbatim term increased compulsive behavior[4]). Two rotigotine subjects discontinued for these compulsive behavior AEs (one recovered, the other lost to follow up) and two continued in the trial without dose changes (one recovered, one outcome not available). The ropinirole subject experienced a compulsive behavior AE of appetite disorder (verbatim term pathological satiety).

4.4 Schwarz's discussion
After summarizing the data, Schwarz concluded that the risk for compulsive behavior was low among rotigotine treated subjects in the development program studies. Schwarz proposed the following labeling statement (location not specified) to address the compulsive behavior risk:

> Compulsive disorders, including pathological gambling, hypersexuality, increased libido, and repetitive meaningless actions (punding), have been observed in subjects treated with Neupro.

[3] This event was not characterized in the narrative provided by Schwarz disease open label (non extension) trials.
[4] This event was not characterized in the narrative provided by Schwarz

4.5 FDA Narrative Review

I read the narratives provided for rotigotine subjects that experienced a compulsive behavior AE. In most cases the narrative provided little information about the event other than the verbatim term. In some cases it was not possible to determine the nature of the event from the narrative (narrative reported only "compulsive behavior"). In some cases, the reported severity of the event did not seem consistent with the reported event. For example, for subject SP515/100301, the narrative noted an event of pathological gambling but the reported severity was mild. In some cases it was difficult to assess the time course of events. For example, in one case (Subject SP512/13707) the narrative stated that the event (pathological gambling) was present prior to enrollment in a controlled trial where the subject received rotigotine but the event was not reported by subject until after the subject had enrolled in an open label extension trial and was therefore considered a treatment emergent event.

One narrative did provide details about the actual event I summarize information from that narrative below.

Subject SP650/13209 was a 40 year old female with no identified history of compulsive behavior. She developed a compulsion to gamble after taking rotigotine 13.5mg for 6 days. The narrative reported that she began gambling online and lost $300,000. The compulsion to gamble resolved after stopping rotigotine and recurred when the subject was treated with pramipexole. The gambling compulsion stopped again when pramipexole was stopped. Concomitant medications at the time of the event were carbidopa/levodopa, selegiline, and acetaminophen/acetylsalicylic acid/caffeine.

4.6 FDA Discussion

Schwarz identified a number of compulsive behavior events in rotigotine treated subjects participating in Parkinson's disease trials, but the data captured on these events is inadequate to support definitive conclusions regarding causality. The compulsive behavior events were not well described in the provided narratives and in some cases the events may have preceded exposure to rotigotine, excluding the drug as a cause. The poor data capture is understandable given that the possibility of a link between compulsive behaviors and Parkinson's disease medications has received attention in the published medical literature only fairly recently. To improve the quality of the data collected, ongoing trials should attempt to capture subjects' histories for compulsive behavior events prior to entering trials, should monitor for the development or worsening of these events during trials, and should capture specific details about the nature of these events.

The presentation suggests that compulsive behavior events occur infrequently but the lack of quality data precludes precise risk estimates. In the Parkinson's disease trials, the risk for compulsive behaviors was <1% among rotigotine subjects. Since Schwarz did not actively monitor for these events, it is possible that the actual risk was higher than that noted. The risk could be underestimated if subjects did not recognize these behaviors as adverse events or purposefully avoided reporting them given the associated social stigma.

The data from the Parkinson's disease controlled trials and from RLS trials provide interesting results that require additional investigation. Schwarz found that there was a numerically higher risk for compulsive behavior events among rotigotine subjects when compared to placebo subjects in Parkinson's disease controlled trials. The comparison is not robust given the low frequency of identified events and the relatively small sample sizes. While these data are suggestive of a causal relationship, additional data are needed to further assess this relationship. The lack of compulsive behavior events in RLS trials is also interesting but again additional information is needed to fully understand the implications of these results. The RLS database includes a different patient population, fewer subjects, and the studies employed lower rotigotine dosages, all of which could have contributed to the lack of identified compulsive behavior cases.

4.7 Labeling Recommendation

I believe that the labeling language recently proposed for the approved Parkinson's disease drugs is appropriate for rotigotine as well. If rotigotine is approved, I recommend that the **Information for Patients** subsection of the **PRECAUTIONS** section of the labeling include the following statement:

> There have been reports of patients experiencing intense urges to gamble, increased sexual urges, and other intense urges while taking one or more of the medications generally used for the treatment of Parkinson's disease, including Neupro. Although it is not proven that the medications caused these events, these urges were reported to have stopped in some cases when the dose was reduced or the medication was stopped. Prescribers should ask patients about the development of new or increased gambling urges, sexual urges or other urges while being treated with Neupro. Patients should inform their physician if they experience new or increased gambling urges, increased sexual urges or other intense urges while taking Neupro. Physicians should consider dose reduction or stopping the medication if a patient develops such urges while taking Neupro.

5.0 APPENDIX

5.1 Summary of Clinical Details from Death Narratives

New Deaths from Early PD trials

Pleural carcinoma
Subject SP513OL/101003 This 67 year old male who was treated with rotigotine for 1145 days (last dose 18mg) died and the reported cause of death was pleural carcinoma, metastatic. This subject had a history of hemorrhoid, irritable colon, vertigo, cervical spondyloarthosis, hypertension, ulcerative colitis, erosive gastritis, insomnia, cataract, prostate adenoma, and urolithiasis. After receiving rotigotine in an RCT he enrolled in an OL extension study. He was diagnosed with metastatic adenocarcinoma of the right pleura along with pleural exudate, atrial fibrillation and respiratory insufficiency. He was treated with morphine, bronchodilators, a diuretic, anxiolytic, and antitussives. The subject died, six days after his last dose of rotigotine.

Sepsis
Subject SP513OL/103406 This 58 year old male who was treated with rotigotine for 1139 days (last dose 18mg) died and the reported cause of death was sepsis. This subject had a history of onichomycosis. He received rotigotine in an RCT and then enrolled in an open label extension study. The subject presented to a hospital with gastroenteritis. Three days later, the gastroenteritis was reported as resolved with sequelae of paralytic ileus and pneumonia. The narrative reported that during the hospitalization for gastroenteritis, the subject had become dehydrated and developed low potassium, ileus, and aspirated while vomiting. The subject was mechanically ventilated and treated with amikacin, amoxicillin/clavulanate, ciprofloxacin, pipracillin/tazobactam, bisoprolol, bromhexine, heparin, metoclopramide, midazolam, neostigmine, potassium, ranitidine, acetylcysteine, and theophylline. Abdominal ultrasound and CT demonstrated enlarged retroperitoneal lymph nodes and a suspected renal tumor (later confirmed as renal carcinoma) on the left side. The subject developed worsening PD symptoms and was reported to be in an akinetic state. The subject developed extensive sacral and heel decubitus ulcers, required a urethral catheter, and continued to have purulent bronchial secretions. The subject developed a fever and had a positive blood culture. He was treated at this time with vancomycin. His neurological condition did not improve. He subsequently underwent surgery for the sacral decubitus ulcer and was withdrawn from the study. The subject died approximately one month later and the reported cause of death was sepsis.

Cardiac Failure
Subject SP513OL/105911 This 61 year old male subject who was treated with rotigotine for 1060 days (last dose ' — _, died and the reported cause of death was cardiac failure. This subject had a history of insomnia, dizziness, enlarged left ventricle, degenerative spine disease, hypertension, coronary artery disease, hyperopia, fracture of costa 8,9,10, and syncope. After completing an RCT where he received rotigotine, the subject enrolled in an open label extension study. The subject developed acute cardiac insufficiency and pulmonary edema. The subject's wife stated that the subject developed dyspnea and an

ambulance was called. The subject died the next day and there were no details about his course or treatment.

Pancreatic neoplasm
Subject SP513OL/106602 This 67 year old male subject who was treated with rotigotine for 1264 days (last dose —) died and the reported cause of death was pancreas neoplasm. The subject had a history of excessive daytime sleepiness, enlarged prostate, and diabetes. After receiving rotigotine in an RCT, he enrolled in an open label extension study. During the study, he was diagnosed with pancreatic cancer and he was treated with radiation and a pancreatic stent. He subsequently developed a gastric hemorrhage and was treated conservatively due to his underlying disease. His pancreatic cancer progressed and the subject died on —

Cerebrovascular disorder
Subject SP513OL/106907 This 73 year old male subject who was treated with rotigotine for 749 days (last dose 18mg) died and the reported cause of death was cerebrovascular disorder. The subject had a history of hypertension, osteoporosis, carpal tunnel syndrome and release surgery. After receiving rotigotine in an RCT, he enrolled in an open label extension study. The subject developed a left sided hemiparesis and was diagnosed with a TIA at an outpatient clinic and was discharged. The family reported that the subject's neurological deficits persisted. The subject died 2 days later and the death was attributed to the stroke. No autopsy was performed.

Respiratory insufficiency
Subject SP513OL/107406 This 82 year old male subject who was treated with rotigotine for 506 days (last dose 18mg) died and the reported cause of death was respiratory insufficiency. This subject had a history of atrial fibrillation, hypertension, reflux esophagitis, and decreased hearing. After receiving ropinirole in an RCT, he enrolled in an open label extension study and received rotigotine. The subject was moved to a nursing home due to declining health. The subject developed respiratory insufficiency and he was not taken to a hospital for treatment. He died at the nursing home. No autopsy was performed.

Myocardial infarction
SP513/108603 This 67 year old male subject who was treated with rotigotine for 609 days (last dose 18mg) died and the reported cause of death was myocardial infarction. This subject had a history of hypertension, herpes zoster, indigestion, osteoarthritis, right knee replacement, and spinal fusion surgeries. After receiving ropinirole in an RCT, he enrolled in an open label extension study and received rotigotine. Rotigotine was last administered on 12/1/04. On — the subject experienced an MI, ruptured ventricular wall, hemopericardium, and died. An autopsy documented a defect in the posterior left ventricular wall with underlying apparently acute infarct, a right intracoronary thrombus and atherosclerosis of the coronary arteries and abdominal aorta.

SP512OL/013405 This 78 year old male subject who was treated with rotigotine for 805 days (last dose 18mg) died and the reported cause of death was myocardial infarction.

This subject had a history of hypertension, hearing loss, hypothyroidism, and deep venous thrombosis. After receiving placebo in an RCT, he enrolled in an open label extension study and received rotigotine. The subject became ill and was taken to a hospital where it was determined he suffered a myocardial infarction. He subsequently died. There were no additional details provided about this event.

SP512OL/013504 This 52 year old male subject who was treated with rotigotine for 992 days (last dose 13.5mg) died and the reported cause of death was myocardial infarction. This subject had a history of hyperlipidemia, hypertension, basal cell carcinoma, inguinal hernia, rotator cuff tear, and carpal tunnel. After receiving placebo in an RCT, he enrolled in an open label extension study and received rotigotine. The narrative noted only that the subject experienced a myocardial infarction and died. The subject was a resident of New Orleans. Following Hurricane Katrina, the medical records and death certificate were requested but not obtained.

Vasculitis
SP630 OL/080412 This 69 year old female who was treated with rotigotine for 99 days (last dose 4.5mg) died and the reported cause of death was rheumatoid vasculitis. This subject had a history of rheumatoid arthritis, breast cancer, diverticulitis, osteoarthritis, cataracts, polymyalgia, pedal edema, UTI, congenital hearing impairment, and seasonal allergies. The narrative reported only that the subject developed vaculitis (no signs or symptoms reported) and was treated with morphine. Her rotigotine dose was tapered. The subject died and there were no additional details provided.

Sudden Death
Respiratory disorder/acute airway obstruction
SP512OL/013102 This 66 year old male subject who was treated with rotigotine for 1049 days (last dose —5) died and the reported cause of death was acute airway obstruction. This subject had a history of dizziness, elevated iron, hypercalcemia, degenerative joint disease, gastroesophageal reflux, angiodysplasia, hypertension, coronary artery disease, and hypercholesterolemia. The subject sat down to lunch and collapsed. Resuscitation attempts by his son and emergency responders were unsuccessful. He arrived at the hospital in asystole and did not respond to CPR, atropine, epinephrine, or lidocaine. He was pronounced dead and the cause of death was cardiopulmonary arrest. The narrative noted that the study ECGs did not demonstrate changes suggestive of coronary artery disease and that the ECG preceding the event had a QTc of 397.

New Deaths from Advanced PD Trials

Motor Vehicle Accident
SP515/101305 This 68 year old male subject who was treated with rotigotine for 27 days during an RCT (last dose 22.5mg) died and the reported cause of death was traffic accident. The subject crossed lanes and drove into oncoming traffic resulting in death. The narrative stated that the subject had not been experiencing sleepiness or dizziness at

the time of the accident. An autopsy found "multiple injuries and that there was no sign of heart or brain disease."

Cerebrovascular disorder
SP515OL/101603 This 78 year old female subject who was treated with rotigotine for 188 days (last dose 27mg) died and the reported cause of death was cerebrovascular accident. This subject had a history of cholelithiasis, pulmonary embolism, atrial fibrillation, and myocardial ischemia. After receiving placebo in an RCT, she enrolled in an open label extension study and received rotigotine. The subject was found on the floor and was subsequently diagnosed as having had a stroke. She did not recover and died approximately 3 weeks after the event. At the time of the event she was taking digoxin, warfarin, furosemide, potassium, lisinopril, and levodopa in addition to rotigotine.

SP650 OL/016225 This 76 year old male subject who was treated with rotigotine for 556 days (last dose 27mg) died and the reported cause of death was cerebrovascular disorder. This subject had a history of coronary artery disease, angioplasty, hepatitis, somnolence, dyspepsia, back pain, and sciatica. During the study the subject experienced chest pain and underwent angioplasty. He had two additional hospitalizations during the study (fever, not feeling well). The subject experienced an intracerebral bleed (right brain, midbrain, and brainstem). The event was reportedly not preceded by a fall or injury. The subject died four days later.

Bronchial Carcinoma
SP515OL/108617 This 76 year old male subject who was treated with rotigotine for 275 days (last dose [redacted]) died and the reported cause of death was bronchial carcinoma. This subject had a history of osteoarthritis and joint dislocation. After receiving rotigotine in an RCT, he enrolled in an open label extension study. During the trial the subject developed chest pain and was subsequently diagnosed with poorly differentiated large cell bronchial carcinoma. The subject died 3 months later.

Intestinal Obstruction
SP515OL/111701 This 83 year old male subject who was treated with rotigotine for 477 days (last dose [redacted]) died and the reported cause of death was intestinal obstruction. This subject had a history of eczema, insomnia, carotid artery stenosis, peripheral edema, arteriosclerosis, prostatic adenoma, hyperuricemia, hypertension, depression, TB, and lipoma. After receiving rotigotine in an RCT, he enrolled in an open label extension study. During the study, the subject developed abdominal pain, nausea, and abdominal dilatation. The subject did not respond to nasogastric suction and subsequently underwent surgery. During the transfer from the stretcher to the operating table, the subject aspirated and experienced cardiac arrest. The subject did not respond to resuscitation efforts and died.

Pulmonary embolism
SP515OL/111912 This 73 year old male subject who was treated with rotigotine for 239 days (last dose 27mg) died and the reported cause of death was pulmonary embolism. This subject had a history of deep vein thrombosis, subdural hematoma, constipation,

UTI, atrophic gastritis, dyslipidemia, insomnia, pain in extremity, depression, supraventricular extrasystoles, orthostatic hypotension, inguinal hernia, tonsillitis, and renal colic. During the trial the subject experienced sudden onset of dyspnea and chest pain. He died that same day. The narrative did not detail how the diagnosis of pulmonary embolism was made.

Pneumonia
SP650 OL/010210 This 78 year old male subject who was treated with rotigotine for 463 days (last dose 13.5mg) died and the reported cause of death was pneumonia. This subject had a history of actinic keratosis, hypertension, constipation, blepharal papilloma, erectile dysfunction, onychomycosis, benign prostatic hyperplasia, peripheral nerve operation, carpal tunnel syndrome, spondylosis, appendectomy, and nephrolithiasis. During the trial, the subject developed shortness of breath and was diagnosed with bacterial pneumonia. Despite treatment with antibiotics, the subject died four days later.

SP650 OL/015811 This 57 year old male subject who was treated with rotigotine for 568 days (last dose 18mg) died and the reported cause of death was pneumonia. This subject had a history of cataract, hypotension, fall, somnolence, drooling, constipation, night sweats, blurred vision, seasonal allergies, dermatitis, cough, ankle fracture, upper limb fracture, and inguinal hernia. After receiving rotigotine in an RCT, he enrolled in an open label extension study. During the study the subject was diagnosed with Hodgkin's lymphoma and was treated with granisetron, doxorubicin, bleomycin, dacarbazine, and vinblastine. Ten months later he developed dyspnea fever, chills and was admitted to a hospital and diagnosed with right lower lobe pneumonia. He was treated with clindamycin, levofloxacin, lansoprazole, ipratropium/albuterol and fluids. Five days after admission he was transferred to a rehabilitation facility and he died 2 days later.

Renal Cell Carcinoma
SP650 OL/010511 This 82 year old male subject who was treated with rotigotine for 541 days (last dose 27mg) died and the reported cause of death was renal cell carcinoma. This subject had a history of anxiety, carotid artery stenosis, angina pectoris, coronary artery disease, myocardial infarction, angioplasty, dizziness, hematuria, chronic renal failure, benign prostatic hyperplasia, transurethral prostatectomy, hypertension, hypercholesterolemia, gastroesophageal reflux, vasovagal syncope, edema, cataract, dyspepsia, drug hypersensitivity, depression, rheumatoid arthritis, bilateral deafness, osteoarthritis, seasonal allergy, back pain, and tonsillectomy. During the trial, he was diagnosed with renal cell carcinoma. He subsequently experienced a GI bleed and then acute respiratory failure and death. No additional details were provided for these events.

Myocardial Infarction
SP650 OL/011602 This 73 year old male subject who was treated with rotigotine for 1096 days (last dose 27mg) died and the reported cause of death was myocardial infarction. This subject had a history of hypertension, somnolence, burning sensation, radical prostatectomy, nocturia, and wrist fracture. During the trial this subject was hospitalized for chest pain and dyspnea and had elevated cardiac enzymes. Cardiac catheterization showed severe coronary artery disease and an echo showed severe mitral

regurgitation. A stent was placed and the subject was transferred to another hospital. The subject underwent 4 vessel bypass surgery and mitral valve repair. This post operative course was complicated by septic shock, renal failure, internal bleeding, and jaundice. The subject subsequently died.

SP650 OL/013109 This 76 year old male subject who was treated with rotigotine for 501 days (last dose 27mg) died and the reported cause of death was myocardial infarction. This subject had a history of hyperlipidemia, irregular heart rate, ventricular extrasystoles, sinus bradycardia, depression, constipation, actinic keratosis, headache, abscess limb, cataract, erectile dysfunction, benign prostatic hyperplasia, hypoacusis, hip arthroplasty, drug hypersensitivity, pilonidal cyst, somnolence, and arthralgia. During the trial the subject experienced an episode of "indigestion" associated with left shoulder pain. He was subsequently found unresponsive. He was admitted to a hospital and myocardial enzymes were elevated and a head CT was negative. He was intubated and mechanically ventilated and treated with heparin, and aspirin. A cardiac catheterization found an occluded circumflex artery and additional vessels with minor disease. The subject subsequently experienced extension of his MI with chest pain and myocardial enzyme elevation and developed ventricular fibrillation that progressed to cardiac arrest and death.

Coronary Artery Disease
SP650 OL/ 013202 This 52 year old male who was treated with rotigotine for 822 days (last dose 22.5mg) had been off study medication for 25 days prior to death and the reported cause of death was coronary artery disease. This subject had a history of tobacco use, cocaine abuse, insomnia, nocturia, limb injuries, meniscus lesion, and arthroscopy. Study ECGs were notable only for a left anterior fascicular block that did not change during the study. The narrative reported only that the patient died due to heart disease.

Suicide
SP824OL/014106 This 73 year old male who was treated with rotigotine for 133 days (last dose 4.5mg) died and the reported cause of death was suicide. This subject had a history of cardiac catheterization, spinal fusion surgery, intervertebral disc surgeries, rotator cuff syndrome, knee operation, arthritis, and allergy to chemicals. The subject had no history of depression but the subject's father had committed suicide and he had a sister with depression. During a de-escalation period (rotigotine being stopped for lack of efficacy) the subject committed suicide (method not documented).

5.2 Summary of Clinical Details from SAE Narratives

Select New SAEs from early PD trials

Hallucinations
Subject 512OL/013403 This 70 year old male was treated with rotigotine and developed hallucinations (dose 27mg, on this dose for 72 days prior to this SAE). Concomitant medications at the time of hallucinations onset were amantadine, selegiline, sildenafil, indomethacin, and acetaminophen. This subject had a history of constipation, diabetes

mellitus, pneumonia, bilateral hearing loss and a right foot burn. The subject developed hallucinations (no description provided) during the study and amantadine was stopped. Hallucinations increased and the patient was not sleeping. Selegiline was stopped but the hallucinations persisted. Rotigotine was then stopped but no outcome was provided.

Subject 513OL/100202 This 80 year old female was treated with rotigotine and developed worsening hallucinations (18mg, on this dose 576 days prior to this SAE). This subject had many AEs during rotigotine treatment including falls, femoral neck fractures, and a wound infection. The narrative includes few details about the hospitalization for hallucinations. The event was called worsening hallucinations (no description provided) and apparently resolved within 10 days without dose adjustment or other therapeutic measures.

Subject 513OL/102601 This 73 year old male was treated with rotigotine and developed hallucinations (dose 18mg, on this dose 740 days at the time of the SAE). This subject had a history of hypercholesterolemia, bilateral deafness, prostatitis, cervical arthrosis, ectropion, appendix inflammation and pleurisy. This subject had received rotigotine in an RCT and enrolled in the extension trial. He developed visual hallucinations. Rotigotine was stopped and the hallucinations resolved without additional intervention. Concomitant medications at the time of this SAE were carbidopa/levodopa. The hallucinations were classified as an SAE because they were considered medically important.

Subject 513OL/103307 This 55 year old male was treated with rotigotine and developed hallucinations with insomnia (dose 18mg, on this dose for 2 days, increased for worsening PD). This subject had a history of depressive mood, mild head injury, hypertension, inguinal hernia, hip arthroses, obesity and nephrolithiasis. The subject reported insomnia and visual and acoustic hallucinations on 4/21/04. Concomitant medications at the onset of this event were metixene and bisoprolol. He underwent a psychiatric examination on 5/29/04 and the diagnosis was organic hallucinations probably due to drug effect. The consultant recommended stopping rotigotine and starting quetiapine. Rotigotine was stopped on 6/5/04 and the hallucinations were reported resolved on 7/6/04 (narrative did not note if quetiapine was started).

Subject 513OL/105203 This 75 year old female subject was treated with rotigotine and developed increased hallucinations and right lower lobe pneumonia (dose 4.5mg, on this dose 315 days at the time of these SAEs). This subject had a history of bilateral sensoneural hearing loss, asthma, osteoporosis, femur fracture, joint pains and constipation. This subject experienced increased hallucinations and was admitted to a hospital with fever. A chest x-ray showed "pneumonic changes" and she was treated with IV antibiotics and was discharged after 4 days. The narrative reported that the hallucinations "had settled down to their previous mild level." Concomitant medications were topical mometasone, nioxin, celecoxib, fluoxetine, levodopa/carbidopa, and rivastigmine.

Sleep attacks

Subject 512OL/012601 This 65 year old female subject was treated with rotigotine and experienced sleep attacks (dose 22.5mg, on this dose 107 days at the time of the SAE). This subject had a history of atypical chest pain, pedal edema, upper respiratory tract infection, shoulder pain, intermittent headaches, neck pain, arthritis-hands, urinary tract infections, cholelithiasis, seasonal allergies, candidiasis, and appendicitis. This subject received rotigotine in an RCT prior to enrolling in the open label extension. This subject fell asleep without warning while driving. The narrative did not report any injuries and stated that trial medication was unchanged.

Subject 513OL/107706 This 56 year old female subject was treated with rotigotine and experienced 2 sleep attacks (dose 22.5mg, on this dose 52 days at the time of the first SAE, 27mg, on this dose for 90 days at the time of the second SAE). This subject had a history of epigastric pain, depression, osteopenia, facial paralysis, dizziness, and hypertension. This subject experienced 2 sleep attacks. The first sleep attack occurred while driving and the subject admitted feeling very tired that day. The subject was taking amitriptyline at the time of this event and the amitriptyline was stopped. The second sleep attack was exactly like the first (except subject no longer taking amitriptyline). Trial medication was continued unchanged. Concomitant medications during the first sleep attack were amitriptyline, atenolol, celecoxib, enalapril, and panprotozole. Concomitant medications during the second sleep attack were atenolol, celecoxib, enalapril/HCTZ, loperamide, and panprotazole.

Application site reaction
Subject 513OL/101110 This 71 year old male subject was treated with rotigotine and experienced an application site reaction (dose 18mg, on this dose 125 days at the time of the SAE). This subject had a history of hypertension, chronic pancreatitis, cholecystitis, presbyacusis, prostate hypertrophy, rhinitis, and ankle fracture. This subject received rotigotine in an RCT prior to enrolling in the extension study. The narrative included no description of the reaction and commented that it was an SAE because it was a medically important event. The medication was stopped and the narrative reported that the event resolved. Concomitant medications at the time of the event were pancrealipase, ginkgo, famotidine, and fosinopril.

Arrhythmia
Subject 512OL/012203 This 76 year old male was treated with rotigotine and experienced an arrhythmia (dose 13.5mg, on this dose 935 days at the time of the SAE). This subject had a history of hypertension, hypercholesterolemia, erectile dysfunction, anxiety, hearing loss, and allergies to penicillin and lidocaine. This subject presented to en emergency department with complaint of episodes of syncope. He was admitted to a hospital and an unspecified test demonstrated a decrease in cardiac output. He had a coronary stent placed and a pacer/defibrillator implanted. He was also treated with clopidogrel. Study ECGs demonstrated QTcF ranging from 423-453msec. He was discharged and the syncope but not the arrhythmia was considered resolved. Trial medication was continued unchanged. Concomitant medications at the time of SAE onset were carbidopa/levodopa and amantadine.

Arrhythmia ventricular
Subject 513OL/105610 Identified as a new event but narrative was summarized in the NDA review, p.17.

Rhabdomyolysis
Subject 513OL/100808 This 79 year old male was treated with rotigotine and developed rhabdomyolysis (dose 22.5mg, on this dose 74 days at the time of the SAE). This subject had a history of diabetes, angina, hypertension, diastolic heart failure, chronic obstructive pulmonary disease, benign prostatic hypertrophy, tendon rupture finger, and concussion. This subject had received rotigotine in an RCT prior to enrolling in the extension trial. The subject fell at home (no LOC), and could not get up, remaining on the floor overnight. He was admitted to a hospital and was diagnosed with a hematoma and rhabdomyolysis. Rhabdomyolysis was resolved the next day. The subject withdrew from the trial for the fall. The subject was taking no additional medications at the time of the fall.

Select New SAEs from Advanced PD Trials

Anemia
Subject 650OL/10203 (Identified in the 5/27/05 Safety Update) This 61 year old male was treated with rotigotine and developed anemia (rotigotine dose 27mg, SAE reported after 219 of open label treatment). This subject had a history of gastric reflux, benign large intestinal polyps, constipation, appendicitis, hemorrhoids, arthritis, groin pain, depression, hypertension, nephrolithiasis, depression, anxiety, benign prostatic hypertrophy, androgen deficiency, and carcinoma of the left ear. The subject experienced a drop in hemoglobin to 8.1mg/dL at open label visit 9. His previous hemoglobin results in this trial were 11.7mg/dL (visit 4) and 11.2mg/dL (visit 6). He was diagnosed with an esophageal ulcer and was transfused with 2 units of PRBC. The anemia was considered resolved and the study treatment was continued. He had a hemoglobin result of 14.9mg/dL (visit 11) while continuing study treatment. Concomitant medications at the time of the SAE were carbidopa/levodopa, selegiline, doxepin, citalopram, doxazosin, testosterone, senna fruit, bisacodyl, and famotidine.

Subject SP516/103504 This 69 year old male was treated with rotigotine and developed anemia (rotigotine dose [redacted], on this dose 174 days at the time of the SAE). This subject had a history of inguinal hernia. This subject's anemia was due to a hemorrhagic gastric ulcer that was attributed to use of NSAIDs. His hemoglobin at the time of the bleed was 6.2mg/dL. The subject's course was complicated by a myocardial infarction. He was transfused and treated for his MI (nitrates, simvastatin, and beta blocker). He continued on trial medication and the events resolved. Concomitant medications at the time of the event were levodopa/carbidopa, and ibuprofen.

Subject SP516/108026 This 46 year old female was treated with rotigotine and developed anemia (rotigotine dose [redacted], on that dose for 48 days at the time of the SAE). This subject had a history of anemia, spinal osteoarthritis, and metrorrhagia. This subject developed a GI bleed and gastroscopy revealed gastritis with ulcers and she was

diagnosed as having helicobacter pylori. No hemoglobin values were available from the time of the SAE. She was transfused and treated with antibiotics and iron supplementation. Trial medication was continued unchanged and the event was reported as resolved. Concomitant medications at the time of the event were amantix, hemofer, levodopa/benserazide, and selerin.

Subject SP516/110803 This 64 year old female was treated with rotigotine and developed anemia (rotigotine dose [redacted] on this dose 65 days at the time of the SAE). This subject had a history of spinal fracture, osteoporosis, thyroid disorder, hypercholesterolemia, anxiety, and depression. The subject presented to an emergency department and was diagnosed with an acute anemia. There were no hemoglobin results available from this event. She was treated with iron and omeprazole and the event was considered resolved. Concomitant medications at the time of the event were aspirin, paroxetine, alprazolam, levothyroxine, difosfonal, amantadine, entacapone, and levodopa/carbidopa.

Application site reactions
Subject SP511/000509 This event was summarized in the NDA review, p.15.

Subject SP511/000101 This 72 year old male was treated with rotigotine and developed an application site reaction (dose 27mg, on this dose for 17 days at the time of the SAE). This subject had a history of hepatitis, hay fever, acne, osteoarthritis, and knee surgery. The reaction was described as redness with pruritis at patch application sites. The narrative noted that the reactions decreased within a few days of patch removal. The narrative reported that no other intervention was necessary. The medication was discontinued and the subject recovered.

Subject SP511/000405 This 62 year old male was treated with rotigotine and developed an application site reaction (dose 18mg, on this dose for 11 days at the time of the SAE). This subject had a history of pallidotomy. The subject developed sensitivity to the trial medication at the application site. The patch sites were red and slightly raised. Trial medication was stopped and the event resolved.

Subject SP516/101309 This 79 year old male was treated with rotigotine and developed an application site reaction (dose [redacted], on this dose for 98 days at the time of the SAE). This subject had a history of gastric ulcer, cataract, diabetes mellitus, hypoacusis, hypermetropia, atrial fibrillation, hypertension, unilateral deafness, and ear infection. The reaction was described as a rash and skin redness limited to patch site with pruritis that led to the subject stopping the study medication and resulted in worsening of his Parkinson's disease symptoms. The reaction resolved without other interventions. Concomitant medications at the time of the event were lisinopril, furosemide, metidigoxin, levodopa/carbidopa, acarabose, and glibenclamide.

Sleep attacks
Subject SP650 part II/14004 This event was summarized in the NDA review, p.16
Subject SP650 part II/14105 This event was summarized in the NDA review, p.16

Subject SP650 part II/10804 This 72 year old male was treated with rotigotine and developed sleep attacks (dose 22.5mg, on this dose for 883 days at the time of the SAE). This subject had a history of somnolence, chronic obstructive airway disease, sinusitis, mitral valve prolapse, hoarseness, and benign prostatic hyperplasia. The subject "blacked out" while driving and went off the road. The subject was not injured. A similar event occurred when the subject was taking ropinirole. Trial medication was interrupted and then restarted at a lower dose. The subject also experienced excessive daytime sleepienss during the previous double blind trial. Concomitant medications at the time of the event were carbidopa/levodopa, and ibuprofen.

Subject SP650 part II/10814 This 54 year old male was treated with rotigotine and developed sleep attacks (dose 27mg, on this dose for 365 days at the time of the SAE). This subject had a history of coronary artery disease s/p CABG, hypercholesterolemia, hypertension, osteomyelitis, depression, arthritis, and renal injury. The subject dozed off at a stoplight and his foot slipped off the brake, causing him to strike the vehicle in front of him. The subject admitted to being up late on previous nights. He had no similar events prior to this one. His rotigotine dose was reduced and the outcome was reported as recovered. Concomitant medications at the time of the event were carbidopa/levodopa, selegiline, ramipril, aspirin, atenolol, simvastatin, enalapril, diphenhydramine, and zolpidem.

Rhabdomyolysis
Subject SP650 part II /13041 This event was summarized in the NDA review, p.21

Subject SP650 part II/010206 This 65 year old male was treated with rotigotine and developed rhabdomyolysis (dose 13.5mg, on this dose for 515 days at the time of the SAE). This subject had a history of musculoskeletal pain, fall, finger amputation, joint injury, hypertension, anxiety, and blepharospasm. After falling (stumbled over a mound of dirt), the subject was unable to get up. He was hospitalized and was diagnosed with rhabdomyolysis. There were few details provided about this event but the narrative noted that the subject recovered. Concomitant medications during this event were caridopa/levodopa, aspirin, amlodipine, sertraline, and amantadine.

Acute Renal Failure
Subject SP650 part II/11602 This event was summarized above under deaths (myocardial infarction).

Subject SP650 part II/13906 This 60 year old male was treated with rotigotine and developed acute renal failure (dose — g, on this dose for 49 days at the time of the SAE). This subject had a history of hypertension, hyperlipidemia, drug hypersensitivity, cholelithiasis, osteoarthritis, and gout. During the trial, the subject developed diarrhea that continued for a week before the subject presented to an emergency department. At the time the subject complained of feeling bloated and lightheaded. The subject was diagnosed as being dehydrated and hypotensive and labs revealed a BUN of 69mg/dL and a creatinine 6mg/dL. The subject was treated with IV fluids, phenazopyridine,

terazosin, and a Foley catheter was placed. The subject recovered and was discharged from the hospital. Study medication was restarted after a brief interruption.

Jaundice
Subject SP650 part II/11602 This event was summarized above under deaths (myocardial infarction).

Arrhythmia
Subject SP650 part II/11702 This 70 year old male was treated with rotigotine and developed an arrhythmia (dose 22.5mg, on this dose for 39 days at the time of the SAE). This subject had a history of myocardial infarction, angioplasty, coronary artery disease, hypercholesterolemia, hypertension, peripheral edema, sexual dysfunction, drug hypersensitivity, depression, somnolence, hip arthroplasty, and dysphagia. The subject presented to an emergency department with complaints of lightheadedness and feeling like he would pass out (no LOC). This was diagnosed as presyncope due to sick sinus syndrome. AN ECG demonstrated bradycardia (no rate provided). The subject had a pacemaker inserted with resolution of symptoms. Trial medication was continued.

AV block
Subject SP650 part II/15902 This 68 year old male was treated with rotigotine and developed AV block (dose 13.5mg, on this dose for 764 days at the time of the SAE). This subject had a history of first degree AV block, hypertension, constipation, myopia, and back pain. The subject was diagnosed with second degree AV block following an ECG reading. His previous trial ECGs showed first degree AV block. He was referred to cardiologist and underwent a pharmacological stress. No other details were provided about this event. Study medication was continued. Concomitant medications were metoprolol, and carbidopa/levodopa.

5.3 Summary of Clinical Details from Discontinuations for Adverse Event Narratives

Select Discontinuations for AE from early PD trials

Elevated SGOT, Elevated SGPT, Elevated GGT
Subject SP512OL 010803 The narrative for the subject discusses only application site reaction and does not mention elevated TAs. This subject was a 52 year old male who received placebo in a preceding RCT and then enrolled in an open label trial. He had a history of hypokinetic syndrome, constipation, urinary dribbling, depression, pericarditis, nasal fracture, and right frontal bone congenital deformity. In the preceding RCT, the subject's screening transaminases were AST 24 U/L, ALT 30 U/L, GGT 43 U/L, and total bilirubin was 1.05mg/dL. His AST and ALT were within normal limits throughout the RCT. His other liver related lab results during the RCT included an elevated total bilirubin of 1.52 mg/dL (ULN 1.29 mg/dL) on visit 8 and 1.64 mg/dL on visit 11 and an elevated GGT of 68 U/L (ULN 65 U/L) on visit 11 (Results from the study report for SP512, NDA submission). The CRF for this subject for the open label trial included transaminase elevations that were listed as AEs (onset 7/6/04) and a checked box for "drug withdrawn" as the action taken. I list this subject's TA and total bilirubin results

from the open label trial below. This subject experienced mild increases in liver related lab results that were resolved (except for GGT) at follow up after rotigotine discontinuation.

Liver Related Lab Results for Subject SP512OL/010803

Date	ASAT *RR 0-42U/L	ALAT *RR 0-48U/L	GGT U/L *RR 0-65 U/L	Total bili RR 0-1.3mg/dL
1/16/03	34	47	95	1.5
7/22/03	32	46	99	1.7
1/6/04	31	50	142	1.3
7/7/04	43	76	114	0.8
10/7/04 (end of study, last dose 10/5/04)	33	46	94	0.8
11/3/04 (follow up off drug)	30	38	76	1.0

*Reference range

Select Discontinuations for AE from Advanced PD trials

Electrocardiogram QT corrected interval prolonged
Subject SP650/13905 This 84 year old male with congestive heart failure, atrial fibrillation, dysphagia, cataracts, decubitus ulcer, right knee replacement, Crohn's disease, prostatic hypertrophy, and multiple other medical problems, developed prolonged QTc during treatment with rotigotine and was withdrawn from the trial. This subject had a baseline QTc of 428msec that increased to 493msec. The subject was withdrawn for this finding (increase QTc of 65msec). The sponsor reported that a subsequent central re-read of the ECG revealed that the baseline QTc was 448msec and therefore the subject did not meet withdrawal criteria for absolute increase in QTc. The narrative also noted that this subject had a QTc result of 516msec. Follow up QTc, after discontinuation of rotigotine was 441msec.

Subject SP516/102805 This 71 year old male with a history of acute cardiac failure, heart valve insufficiency, pedal edema, and lymphopenia discontinued from a rotigotine trial for prolonged QTc interval. His baseline QTc was 462msec and during a prior controlled trial (SP515) where he received rotigotine, his ECG was read as borderline QT interval on multiple occasions. The subject had QTc intervals of 413 and 410 on visits 2 and 4, respectively. On visit 8, the subject had a QTc of 531msec. He continued in the study and had QTc results that ranged from 488-519msec. Rotigotine was stopped and a follow up ECG revealed a QTc of 495msec.

Arrhythmia
Subject SP710/12207 This 62 year old female with RLS and a history of cardiac arrhythmia, hypertension, and thyroid carcinoma experienced an AE of arrhythmia that was not classified. The arrhythmia ("rhythm disturbances") occurred at night and with physical strain. No ECG was recorded on the day of the event and no therapeutic measures were used to treat the arrhythmia. She was evaluated by a cardiologist and an

ECG at that visit did not capture an arrhythmia. The subject withdrew from the trial for this event.

Tachycardia
Subject SP824/14812 This 60 year old female with chronic constipation, GERD, migraine, hysterectomy, osteoporosis, eczema, and other medical problems discontinued from a rotigotine trial for tachycardia and insomnia. At the onset of tachycardia, the subject was treated with 13.5mg/day and had received that dose for 1 day. The narrative reported that the baseline ECG was normal but that the subject developed tachycardia during the study (not quantified). Rotigotine was stopped and the subject recovered. The CRF for this subject reported that the onset date for this event was 3/24/05. The vital signs from that day reported 4 pulse rates, all 68 beats per minute. The vital signs recorded on the End of Treatment sheet included pulse rates of 68, 76, and 80 beats per minute. Neither the narrative, nor the CRF include heart rate measures that suggest tachycardia.

Bullous Eruption
Subject SP511/0509/12047 This 53 year old male received rotigotine 18mg/day for 23 days when he days when he developed blistering of the skin under 2 patches. The lesions were circumscribed and limited to the patch sites. The narrative also described erosions, oozing, reddening, and crusting. The subject withdrew from the study and the outcome was reported as resolved.

Sleep Attack
Subject SP650/14105 This event was summarized in the NDA Safety Review, p.16.

Hepatic Enzymes Increased
Subject SP650/013905 This subject was described above as discontinuing for QT prolongation. This subject also experienced an increase in GGT to 141U/L (baseline 21 U/L) and alkaline phosphatase to 132U/L (baseline 82 U/L). The elevated GGT and ALP were considered non-serious events and were reported as resolved.

Select Discontinuations from RLS studies

Hepatic enzymes increased
Subject SP709/012904 This 67 year old female was treated with rotigotine and discontinued from a trial for an AE of hepatic enzymes increased. At the time of discontinuation from this open label trial she was treated with rotigotine 6.75mg and had been receiving that dose for 196 days. This subject had received rotigotine in a preceding RCT. The narrative commented that this subject experienced elevated ALT, GGT, LDH, and ferritin but provided only GGT results of 158U/L and 132 U/L (ULN 49U/L). In the table below, I list this subject's TA and total bilirubin results from the open label trial below as provided in the CRF.

Liver Related Lab Results for Subject SP709/012904

Date	ASAT	ALAT	GGT	Total bili

	*RR 11-37 U/L	*RR 8-43 U/L	*RR 8-49 U/L	*RR 0.22-1.28 mg/dL
3/3/04 (visit 5)	28	43	73	0.3
9/7/04 (visit 11)	33	54	158	0.2
9/14/04 (unscheduled visit)	34	56	132	0.33

* Reference Range

Trial medication was stopped on 9/21/04 and the subject was lost to follow up. The only noted concomitant medication was nifedipine.

QT increased

Subject SP709/010423 This 63 year old male was treated with rotigotine and discontinued from a trial for increased QTc. This subject was treated with rotigotine 4.5mg and had been on this dose for 8 days (previously on 6.25mg). This subject had a history of cardiac dysrrhythmia, pacemaker insertion, arthritis, endoprosthesis, reflux esophagitis, and myopia. During the titration period of the trial the subject was noted to have an increase in QTcB. The subject had a screening QTcB of 444msec and a baseline QTcBs of 409msec, 419msec, and 455msec. On visit 3, the day of the noted increase, his QTcB was 501msec (trial medication stopped following the result). Visit 8 (one week after stopping rotigotine) and visit 9 (2 weeks after stopping rotigotine) QTcBs were 446msec and 438msec, respectively. Concomitant medications during the trial were levodopa/carbidopa, cabergoline, trimipramine as needed, esomeprazole, and metoclopramide.

5.4 Differences between Original Coding and Cardiologist Coding for Cardiac Arrhythmia AE Analysis

Original Preferred Term	Cardiologist Preferred Term	N
Arrhythmia	Not coded	1
	Arrhythmia	3
	Extrasystoles	1
	Palpitations	2
	Ventricular extrasystoles	1
Atrial bigeminy	Atrial bigeminy	3
	Ventricular extrasystoles	1
Atrial fibrillation	Not coded	2
	Arrhythmia	1
	Atrial fibrillation	32
Atrial flutter	Not coded	4
	Atrial flutter	6
Atrial tachycardia	Not coded	1
Atrioventricular block	Bundle branch block bilateral	1
Atrioventricular block complete	Atrioventricular block complete	1

Atrioventricular block 1st degree	Not coded	1
	Atrioventricular block 1st degree	26
	Electrocardiogram T wave inversion	1
Atrioventricular block 2nd degree	Atrioventricular block 2nd degree	1
	Supraventricular extrasystoles	1
Bifascicular block	Bifascicular block	1
Bradycardia	Bradycardia	8
	Sinus bradycardia	2
Bundle branch block	Not coded	1
Bundle branch block left	Not coded	2
	Bundle branch block left	8
	QRS axis abnormal	9
Bundle branch block right	Not coded	2
	Bundle branch block right	10
	Electrocardiogram QRS prolonged	1
Cardiac disorder	Cardiac disorder	1
Cardiovascular disorder	Cardiovascular disorder	2
Electrocardiogram	Not coded	1
Electrocardiogram Q wave abnormal	Electrocardiogram Q wave abnormal	1
Electrocardiogram QRS prolonged	Electrocardiogram QRS prolonged	1
Electrocardiogram QTc interval prolonged	Not coded	11
	Electrocardiogram QTc interval prolonged	21
Electrocardiogram ST segment abnormal	Electrocardiogram ST segment abnormal	1
Electrocardiogram ST segment depression	Electrocardiogram ST segment depression	4
	Electrocardiogram T wave inversion	1
Electrocardiogram ST-T segment abnormal	Electrocardiogram ST segment depression	1
	Electrocardiogram ST-T segment abnormal	2
Electrocardiogram T wave abnormal	Not coded	2
	Electrocardiogram T wave abnormal	8
Electrocardiogram T wave amplitude decreased	Electrocardiogram T wave amplitude decreased	1
Electrocardiogram T wave inversion	Electrocardiogram T wave inversion	1
Electrocardiogram abnormal	Not coded	1
	Atrioventricular block 1st degree	1
	Electrocardiogram abnormal	4

Electrocardiogram change	Not coded	1
	Electrocardiogram change	1
Electrocardiogram poor R wave progression	Electrocardiogram poor R wave progression	2
Extrasystoles	Not coded	1
	Extrasystoles	5
	Supraventricular extrasystoles	1
Heart rate increased	Heart rate increased	1
	Tachycardia	6
Heart rate irregular	Heart rate irregular	7
	Palpitations	1
Nodal rhythm	Nodal rhythm	2
Palpitations	Palpitations	40
	Supraventricular extrasystoles	1
QRS axis abnormal	QRS axis abnormal	2
Sick sinus syndrome	Sick sinus syndrome	3
Sinoatrial block	Supraventricular extrasystoles	1
Sinus arrhythmia	Sinus arrhythmia	2
	Supraventricular extrasystoles	1
Sinus bradycardia	Not coded	9
	QRS axis abnormal	1
	Sinus bradycardia	3
Sinus tachycardia	Not coded	3
	Sinus bradycardia	1
	Sinus tachycardia	8
Sudden death	Sudden death	1
Supraventricular extrasystoles	Supraventricular extrasystoles	5
Supraventricular tachycardia	Arrhythmia	1
	Supraventricular tachycardia	3
Tachycardia	Palpitations	1
	Tachycardia	30
Tachycardia paroxysmal	Tachycardia paroxysmal	1
Ventricular arrhythmia	Ventricular arrhythmia	1
Ventricular extrasystoles	Atrial bigeminy	1

	Supraventricular extrasystoles	1
	Ventricular extrasystoles	17
Ventricular tachycardia	Ventricular tachycardia	3

Source: Listing 3d.2, pp. 1181-1186.

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/s/

Jerry Boehm
4/16/2007 12:33:33 PM
MEDICAL OFFICER

Alice T. Hughes
4/16/2007 01:01:03 PM
MEDICAL OFFICER

CLINICAL EFFICACY REVIEW

Application Type	21829
Submission Number	000
Submission Code	RS with AM
Letter Date	1/19/05
Stamp Date	1/24/05
PDUFA Goal Date	2/28/06
Reviewer Name	Leonard P. Kapcala, M.D.
Review Completion Date	2/28/06
Established Name	rotigotine
(Proposed) Trade Name	Neupro
Therapeutic Class	dopaminergic agonist
Applicant	Schwarz Pharma
Priority Designation	S
Formulation	transdermal patch
Dosing Regimen	4.5 mg patch applied initially daily and titrate dose at weekly intervals by 4.5 mg patch increments up to maximal dose of – mg daily
Indication	Treatment of signs and symptoms of early-stage idiopathic Parkinson's disease (i.e. patients not taking levodopa)
Intended Population	Early Parkinson's Disease

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

My recommendation related to a regulatory 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.

The regulatory action should be based upon the comprehensive consideration of all reviews including my efficacy review and other reviews (safety, statistical clinical pharmacology/biopharmaceutical, pharmacology/toxicology, chemistry).

1.2 Recommendation on Postmarketing Actions

I am not aware of any recommendations for proposed post-marketing risk management plan.

1.2.1 Risk Management Activity

I do not have any particular comments related to risk management activity, particularly because I did not conduct the safety review of rotigotine.

1.2.2 Required Phase 4 Commitments

Reference should be made to other reviews.

1.2.3 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.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The efficacy review is based upon 3 "large" randomized, double-blinded, placebo-controlled mutlicenter trials. Although the sponsor considered studies 512 (also referred to as SP512) and 513 (also referred to as SP512) to be pivotal trials and study 506 (also referred to as SP506) to be a supportive trial, I essentially consider all 3 to be pivotal trials. Studies 512 and 513 were flexible dose (4.5, 9, 13.5, or 18 mg daily rotigotine) trials of approximately 6 and 9 months duration respectively and study 506 in which patients were randomized to placebo or one of several fixed rotigotine doses (4.5, 9. 13.5, 18 mg daily) was conducted over nearly 3 months. Technically, study 506 in which the primary efficacy data were collected over a period up to 11 weeks was slightly shorter than the typical minimal duration ("3 months" or 12 weeks) that we ordinarily require for a "pivotal" study. Study 512 was conducted in North America (U.S. and Canada) and study 513 was conducted in Europe (including central and eastern), Australia/new Zealand, Israel, and Africa and also included an active comparator treatment arm of a dopaminergic agonist, ropinirole, approved in the U.S. and many countries globally.

1.3.2 Efficacy

Clinical Studies

The effectiveness of Neupro™ (rotigotine) in the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease was evaluated in a multinational drug development program consisting of three parallel group, randomized, double-blind placebo controlled studies (506, 512, and 513). These trials were conducted in patients who were not receiving concomitant dopamine agonist therapy and were either L-dopa naïve or previous L-dopa treatment had not occurred within 28 days of baseline or was $\leq$ 6 months in duration for previous treatment. Patients had been excluded from study if they had a history of pallidotomy, thalamotomy, deep brain stimulation, or fetal tissue transplant. Patients receiving selegiline, anticholinergic agents, or amantadine, must have been on a stable dose for at least 28 days prior to baseline and must have maintained that dose for the duration of the trial.

The primary outcome assessment was the change from baseline for the combined scores for Part II (activities of daily living component/subscale)plus part III (motor component/subscale)of the Unified Parkinson's Disease Rating Scale (UPDRS). Part II of the UPDRS contains 13 questions relating to activities of daily living, which are scored from 0 (normal) to 4 (maximal severity) for a maximum (worst) score of 52. Part III of the UPDRS contains 27 questions (for 14 items) and is scored as described for Part II. Part III is designed to assess the severity of the cardinal motor findings in patients with Parkinson's disease (e.g., tremor, rigidity, bradykinesia, postural instability), scored for different body regions, and has a maximum (worst) score of 108.

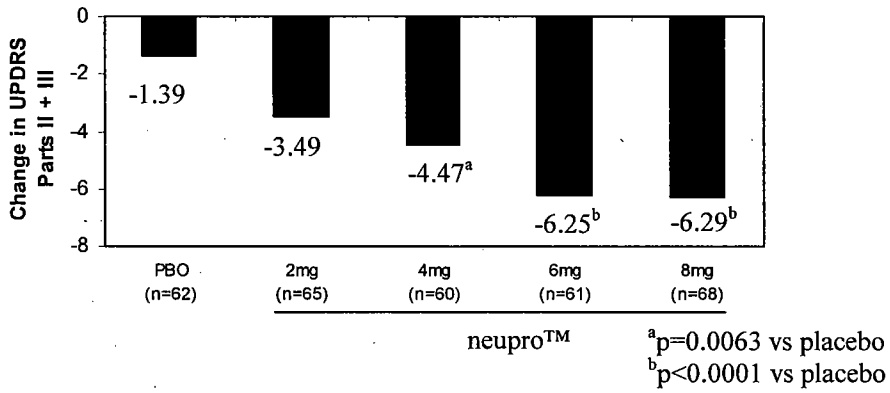
Study 506

Study 506 was a randomized, double-blinded, dose-finding, multicenter, multinational study in which 316 early stage, idiopathic Parkinson's Disease patients were assigned to treatment with either placebo, or one of several fixed doses (4.5 mg, 9 mg, 13.5 mg, or 18 mg per 24 hrs) of Neupro™ for a period up to 12 weeks. This study was conducted predominantly in North American (U.S. and Canada) sites but also included sites in several foreign countries outside of North America. 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 Neupro™ patches over 4 weeks such that the randomized, target dose treatment of Neupro™ 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/10 cm^2 decrement of Neupro™ or placebo) at a time was permitted for intolerable adverse events. Depending on randomized dose assignment, patients received Neupro™ 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.

The mean age of patients was approximately 60 years old (range 34 -83 years; approximately 36 % were $\geq$ 65 years) and the study enrolled more men (61 %) than women (39 %). Most patients (85 %) were Caucasian and most randomized patients ($\geq$ 85 %) completed the full treatment period.

Mean baseline combined UPDRS (Parts II + III) score was similar across all treatment groups. More specifically, this baseline score was 28.0 for placebo, and 28.5, 28.5, 27.6, and 27.1 for the 4.5 mg, 9 mg, 13.5 mg, and 18 mg groups, respectively. Mean changes in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of week 11 or last visit for patients discontinuing early) for the Neupro™ groups were - 3.49, - 4.47, - 6.25 and - 6.29 for the 4.5 mg, 9 mg, 13.5 mg, and 18 mg doses, respectively, and mean change from baseline for placebo was - 1.39 (see Figure 1). A reduction in this score represents improvement and a beneficial change from baseline appears as a negative number. For statistical assessments, an ANCOVA analysis was used and applied the intent to treat principle in which the last observed efficacy data were carried forward when data were missing at the end of 11 weeks treatment. Neupro™ treatment was associated with a clear dose response for the primary efficacy endpoint. The lowest dose group (4.5 mg) showed a numerical reduction in combined UPDRS (Parts II + III) from baseline, and higher dose groups (9 mg, 13.5 mg) showed progressive, beneficial reductions in this endpoint such that a maximal therapeutic effect occurred at 13.5 mg based upon similar primary efficacy results for the 13.5 and 18 mg doses. Although the lowest dose (4.5 mg) showed a mild-moderate, numerical treatment effect, this effect was not statistically significant. The mean changes for the 9 mg, 13.5 mg, and 18 mg doses were statistically significant compared to placebo (see Figure 1).

Figure 1 Study 506: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population



[a]p=0.0063 vs placebo
[b]p<0.0001 vs placebo

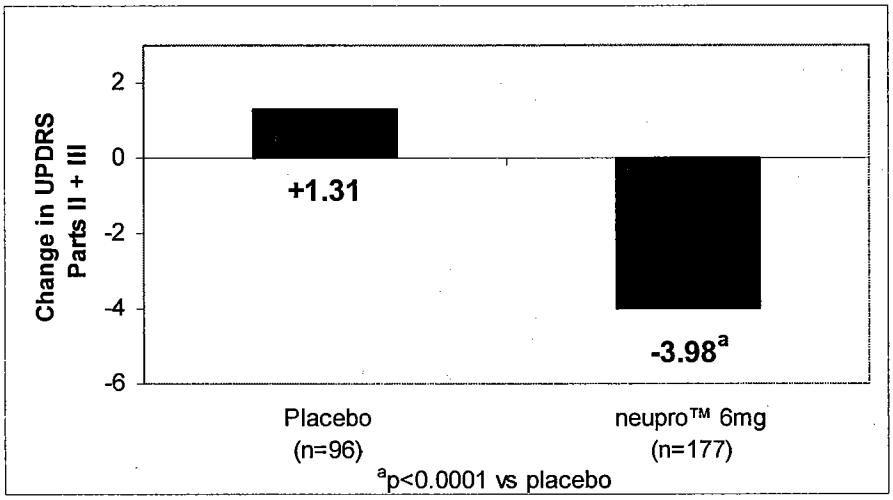
Study 512

Study 512 was a randomized, double-blinded, multicenter, multinational, flexible Neupro™ dose (rotigotine 4.5, 9.0, or 13.5 mg per 24 hours), parallel group study in which 273 early stage, idiopathic Parkinson's Disease patients were assigned (2: 1 ratio of Neupro™ : placebo) to treatment with either placebo or Neupro™ for a period up to about 28 weeks. This study was conducted in 50 sites in North America (U.S. and Canada). Patches were applied to different body parts including upper or lower abdomen, 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/10 cm^2 decrement of Neupro™ 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.

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.

Mean baseline combined UPDRS (Parts II + III) was similar in both groups (29.9-Neupro™ group, 30.0-placebo). Neupro™ treated patients experienced a mean decrease in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 27 or last visit for patients discontinuing early) of -3.98, and placebo treated patients showed a mean change from baseline of + 1.39 (see Figure 2), representing a beneficial treatment effect (i.e. mean Neupro™ effect – mean placebo effect) of – 5.37. A reduction in this score represents improvement and a beneficial change from baseline appears as a negative number. For statistical assessments, an ANCOVA analysis was used and applied the intent to treat principle in which the last observed efficacy data were carried forward when data were missing at the end of 27 weeks treatment.

Figure 2 **Study 512: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population**



Study 513

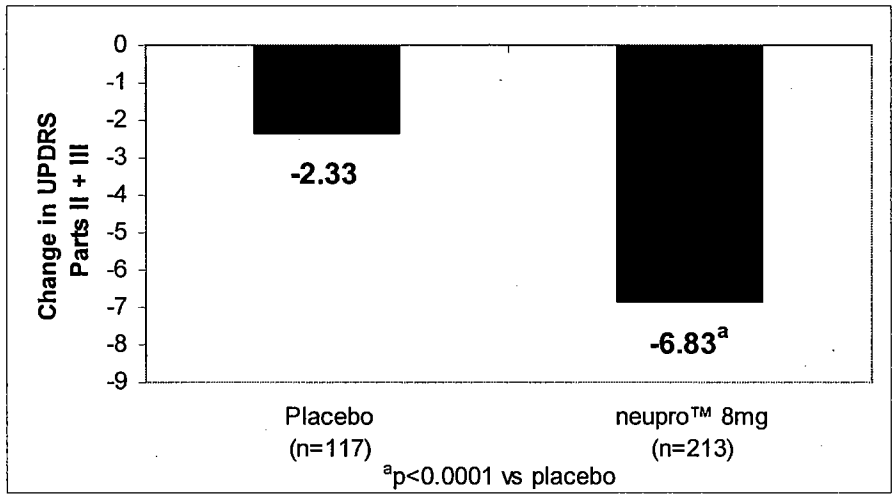
Study 513 was a randomized, double-blinded, multicenter, multinational, flexible Neupro™ dose (rotigotine 4.5, 9.0, 13.5, or 18 mg per 24 hours), 3 arm, parallel group, study using a double-dummy treatment in which 561 early stage, idiopathic Parkinson's Disease patients were assigned to treatment with either placebo or Neupro™ or active comparator (i.e. ropinirole) in a ratio of 1 : 2 : 2 for a period up to about 39 weeks. 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, 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/10 cm^2 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. Ropinirole or placebo capsules were administered TID, preferably with meals. 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. 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.

The mean age of patients was approximately 61 years old (range 30 -86 years; approximately 41 % were $\geq$ 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. The mean daily dose of Neupro™ was about 17 mg and approximately 90 % of patients achieved the maximal daily dose of 18 mg.

Mean baseline combined UPDRS (Parts II + III) was similar across all groups (33.2-Neupro™, 31.3-placebo, 32.2-ropinirole). Neupro™ treated patients experienced a mean decrease in the combined UPDRS (Parts II + III) from baseline to end of treatment (end of treatment week 37 or last visit for patients discontinuing early) of - 6.83, and placebo treated patients showed a mean change from baseline of – 2.33 (see Figure 3), representing a beneficial treatment effect (i.e. mean Neupro™ effect – mean placebo effect) of – 4.50. A reduction in this score represents improvement and a beneficial change from baseline appears as a negative number. For statistical assessments, an ANCOVA analysis was used and applied the intent to treat principle in which the last observed efficacy data were carried forward when data were missing at the end of 37 weeks treatment.

Figure 3 Study 513: Mean Change in UPDRS (Parts II + III) from Baseline at End of Treatment for Intent-to-Treat Population



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 $\geq$ 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.

- If approval of rotigotine is granted for treatment of early Parkinson's Disease, I recommend that the 4.5 mg (10 cm^2), 9 mg (10 cm^2), and 13.5 mg (30 cm^2) patches strengths be approved because these strengths were studied in at least one of the 3 pivotal trials. It does not appear that the 18 mg (40 cm^2) patch strength was studied in any pivotal trial. It is also relevant to note that, on average, the 4.5 mg, 9 mg, 13.5 mg, and 18 mg patches (containing the specified content of rotigotine) delivered approximately 2, 4, 6, and 8 mg of rotigotine, respectively.

1.3.3 Safety

The following is a summary of safety findings abstracted from the Executive Summary of the safety team review :

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 patch1. 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 chronically 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%, 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.

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 . labeling

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

; 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.

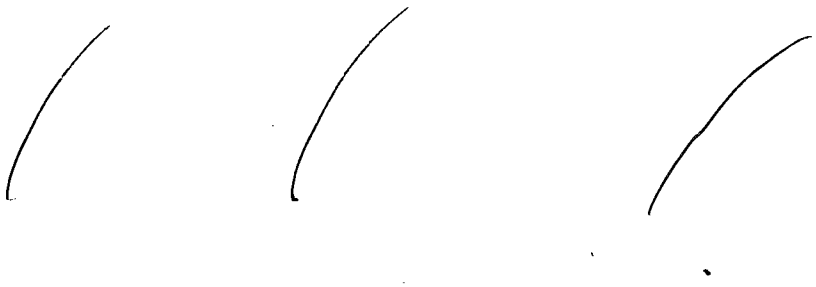
Without robust head to head studies, there is insufficient data to make definitive safety comparisons among the dopamine agonists used to treat PD. The patch delivery system may offer an advantage in patients having difficulty with taking oral medication but it will also carry the risk of application 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.

1 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process



1.3.5 Drug-Drug Interactions

The Clinical Pharmacology/Biopharmaceutical review describes information about potential drug-drug interactions.

1.3.6 Special Populations

The Clinical Pharmacology/Biopharmaceutical review describes information about special populations.

APPEARS THIS WAY
ON ORIGINAL

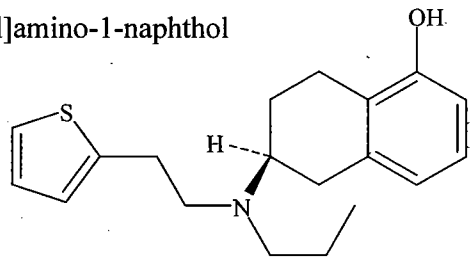
2 INTRODUCTION AND BACKGROUND

2.1 Product Information

a) Proprietary Name: Neupro
b) Non-Proprietary Name (USAN): rotigotine
c) Code Name/#: SPM 962

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT :

(-)-(*S*)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino-1-naphthol
$C_{19}H_{25}NOS$ Formula Weight 315.47



Neupro (rotigotine transdermal system) is an adhesive patch available in — strengths consisting of three layers. The first layer, the backing film, is a flexible, beige to light brown colored backing film, — The second layer is the drug matrix. The drug matrix consists of — povidone and rotigotine with sodium bisulfite, ascorbyl palmitate and *dl*-α-tocopherol. — The third layer is a protective foil that consists of a — film that is coated on one side with a fluoro-polymer. The fluoro-polymer contacts the drug/adhesive matrix. The patch is applied to the skin of the patient (thighs, abdomen or upper arms) once daily at approximately the same time. (The liner is removed and the new patch is placed in a location different from the previous patch that is removed.) The patches are packaged in — pouches, —

The drug substance content of the patch exceeds the delivered dose. The dose is proportional to the area of the patch. The composition of the drug/adhesive matrix is identical for all strengths.

Dose	Patch area	Drug content of the patch
2 mg	10 cm^2	4.50 mg
4 mg	20 cm^2	9.00 mg
6 mg	30 cm^2	13.5 mg

The drug product is manufactured by LTS Lohmann Therapie-Systeme AG of Andernach, Germany. Drug product matrix is made by

Drug product specifications include tests for

The Chemistry review by Dr Tom Broadbent noted that release results of the validation batches (three batches of each strength) are adequate and that all samples complied with acceptance criteria.

Two degradation products, and are thus qualified. another degradation product, is considered an unqualified impurity. The limits for other single impurities and of the 4.5 and 9 mg dermal patches are based upon the ICH Q3B qualification threshold (< maximum daily dose). The limits for the unqualified degradation products are reduced according to patch size and the ICH Q3B threshold. All impurities ≥ are reported.

Limits of Degradation Products (Stability Limits)

Impurity Patch size	4.5 mg/10 cm²	9 mg/20 cm²	13.5 mg/30 cm²
	NMT	NMT	NMT
	NMT	NMT	NMT
	NMT	NMT	NMT
Another single impurity (except synthesis impurities)	NMT	NMT	NMT
Total degradation products	NMT	NMT	NMT

The Chemistry review by Dr. Tom Broadbent noted that product labeling is acceptable with one exception. He noted that product labeling should provide warning that the product contains sodium bisulfite, according to 21 CFR 201.22 (a) and (b). He further noted that it is understood that the amount of sodium bisulfite in the product (if there is any at all) is very low; however, the regulation makes no exception according to the amount or dosage form.

Rotigotine is a non-ergolinic $D_3/D_2/D_1$ dopaminergic agonist for the treatment of Parkinson's disease. Although it is thought that mechanism of action of rotigotine may be related to simultaneous activation of the D_3, D_2, and D_1 dopaminergic receptor subtypes in the caudate-putamen in the brain, the precise mechanism of action of rotigotine as a treatment for Parkinson's disease is not definitely known.

Sponsor's Proposed Indication, Dosing Regimen, and Age Groups

Rotigotine (Neupro™) is indicated for the treatment of the signs and symptoms of early-stage idiopathic Parkinson's disease (i.e. patients not taking levodopa)

A single daily dose should be initiated at a 4.5 mg patch/24 hrs and then increased in weekly patch increments of 4.5 mg/24 hrs as needed to an effective dose of 4.5, 9, 13.5 — mg. The sponsor notes that treatment benefits began as early as the second week of treatment. If it is necessary to discontinue use of rotigotine, it should be discontinued gradually. The daily dose is supposed to be reduced by a 4.5 mg patch/24 hrs with a dose reduction preferably every other day, until complete withdrawal of rotigotine.

Rotigotine is applied once-a-day. The adhesive side of the transdermal system should be applied to clean, dry, intact healthy skin on the front of the abdomen, thigh, hip, flank, shoulder, or upper arm. The transdermal system should be applied at approximately the same time every day, at a convenient time for the patient. Because rotigotine is administered transdermally, no effect of food is expected and it can be applied irrespective of the timing of meals. The application site for rotigotine should be moved on a daily basis (for example, from the right side to the left side and from the upper body to the lower body). Rotigotine should not be applied to the same application site more than once every 14 days and should not be placed on skin that is oily, irritated, or damaged, or where it will be rubbed by tight clothing. If it is necessary to apply rotigotine to a hairy area, the area should be shaved at least 3 days prior to rotigotine application. The system should be applied immediately after opening the pouch and removing the protective liner. The system should be pressed firmly in place for 20-30 seconds, making sure there is good contact, especially around the edges. If the patient forgets to replace rotigotine, or if the transdermal system becomes dislodged, another transdermal system should be applied for the remainder of the day.

Rotigotine is to be used by adults and has not been studied for a treatment effect in pediatric patients who do not develop idiopathic Parkinson's Disease. Rotigotine has been studied in geriatric patients (≥ 65 years) and efficacy has been shown. There is no recommendation for dose adjustment in geriatric/elderly patients.

2.2 Currently Available Treatment for Indications

Levodopa (LD) and Compounds Prolonging the Effects of LD

In the mid-1960's, it was discovered that Parkinson's disease was caused by a deficit ofdopamine in the brain. Subsequently, the discovery that levodopa (LD), an amino acid precursor to dopamine, was able to replenish the depleted neural dopamine and greatly ameliorate the symptoms of Parkinson's disease has been considered a major advancement in medical treatment. These findings revolutionized the management of Parkinson's disease. Subsequently, many other therapeutic advances have been made that further enhanced the management of Parkinson's disease. These advances included the introduction of : 1) peripheral dopa decarboxylase inhibitors (DDI) such as carbidopa (approved in U.S.) and benzerazide (used

outside the U.S.); 2) catecholamine-O-methyl transferase (COMT) inhibitors (e.g. entacapone and tolcapone); and 3) monoamine oxidase-B inhibitors (MAO-B inhibitors), selegiline is the only MAO-B inhibitor approved for Parkinson's Disease in the U.S. All of these drugs are considered to prolong the half-life of endogenous and exogenous LD and/or dopamine and, thus, prolong the action of dopamine at the receptor.

LD has been the most important drug treatment of Parkinson's disease for more than 3 decades. However, chronic LD therapy is associated with the development of adverse effects in the majority of patients. These include motor fluctuations, dyskinesias, and neuropsychiatric problems. The extent to which these symptoms represent progression of the disease and how much they may relate to LD therapy is not known. Recent evidence, however, suggests treatment with agonists may delay the onset of dyskinesia. Other clinical features (e.g. "freezing" and dementia) develop with the progression of the disease and do not respond to LD. Gradually, after several years of LD therapy, the duration of therapeutic benefit (i.e. "on" period) from LD progressively shortens, and the lack of therapeutic benefit (i.e. "off" period) is prolonged. During the early (first few) years, motor fluctuations are predictably associated with the dosing time of LD. However, as the motor fluctuations become more troublesome, some occurrences of motor fluctuations become less predictable in their timing in relationship to LD intake, especially "freezing-in-place." Dyskinesias also are commonly associated with LD therapy. Initially the dyskinesias are mild and not disabling but usually progress to become severely disabling. The incidence and severity of the dyskinesias are believed to increase not only with the duration of LD therapy but also with the daily dose. Although the pathophysiological mechanism responsible for the development of these motor complications in patients chronically treated with LD is not considered to be known, the pulsatile stimulation of dopamine receptors resulting from administration of several daily doses of LD and the increase of oxidative stress has been implicated by several researchers as possibly responsible.

Amantadine

The antiparkinsonian effects of amantadine were discovered almost 35 years ago, when a patient with Parkinson's disease took this drug as influenza A prophylaxis. The mechanism of action of amantadine in Parkinson's disease is not clear, but much evidence suggests that its effects are mediated through the dopamine system and additionally, through the inhibition of N-methyl-D-aspartate (NMDA) receptors. Amantadine has been used both in early-stage Parkinson's disease as monotherapy and as adjunctive therapy to LD in advanced-stage disease. Gastrointestinal discomfort, nausea, sleep disturbance, hallucinations, and nervousness are frequent side effects of amantadine.

Anticholinergics

Anticholinergics were introduced in treatment of post-encephalitic parkinsonism and idiopathic Parkinson's disease in the mid- to late-1920s. Their beneficial effects are mediated by blockade of the central nervous system (CNS) muscarinic acetylcholine receptors. Anticholinergics are used as monotherapy in untreated, early-stage Parkinson's disease and as adjunct therapy in

patients already on other therapies. These medications appear to provide the most benefit with rigidity and tremor. Peripheral side effects include dry mouth, blurred vision, and constipation, whereas central side effects include dizziness, confusion, memory loss, hallucinations, and dyskinesia. These adverse events are more frequent in the elderly patients

Monoamine Oxidase Inhibitors

Monoamine oxidases (MAO; isozymes A and B) are intracellular enzymes that play a role in the catabolism of neuroactive amines such as dopamine; inhibitors of the enzyme provide benefit in Parkinson's disease. The most widely used compound in this group for treatment of Parkinson's disease is selegiline, a selective, irreversible inhibitor of MAO B. Selegiline monotherapy provides modest symptomatic benefit in early-stage Parkinson's disease and allows symptomatic control with lower LD doses in advanced stages of Parkinson's disease. The most frequent side effects are increase in dyskinesia, nausea, dizziness, dryness of mouth, sleep disturbances, confusion, anxiety, hallucinations, and orthostatic hypotension.

Dopaminergic Agonists

In comparison with LD, dopaminergic agonists selectively interact with specific dopaminergic and non-dopaminergic receptor subtypes. During the past several years, considerable evidence suggests that motor fluctuations and dyskinesias may be more related to the duration of LD therapy than to disease progression. Therefore, newly introduced oral dopaminergic agonists have received widespread clinical acceptance because they can not only delay the initiation of LD therapy, but also because their use might delay progression of the disease and the onset of motor complications. A survey of the available scientific literature and the current market suggests that these dopamine agonists are gaining acceptance as the drug of choice not only for advanced-stage, idiopathic Parkinson's disease but also for the initial treatment of drug treatment-naïve Parkinson patients. Taking these findings into account, guidelines published in the American Academy of Neurology journal, Neurology, suggest the use of dopaminergic agonists as a possible first-line treatment over LD in Parkinson's disease. This is a change from earlier therapeutic concepts, which were primarily based on the use of LD.

In general, the non-ergolinic compounds pramipexole and ropinirole are relatively selective in stimulating D_2 and D_3 dopaminergic receptor subtypes and have a better side effect profile than the ergolinic dopamine agonists such as bromocriptine (approved for Parkinson's Disease in U.S), pergolide (approved for Parkinson's Disease in U.S), lisuride, and cabergoline. Both ergot and non-ergot dopamine agonists share a variety of peripheral and central adverse affects. The most common "peripheral" dopaminergic adverse events are nausea, vomiting and orthostatic hypotension. Central dopaminergic adverse events are dominated by psychiatric symptoms, similar to LD. They include mood disturbances (such as depression, irritability, euphoria, and hypomania), inappropriate sexual behavior, hallucinations, delusions, agitation, confusion, and paranoid psychosis. Other reactions, which are common to all dopamine agonists are peripheral edema and reduction of anterior pituitary hormone secretion, particularly prolactin. Ergot derivatives are associated with pleuropulmonary, cardiac (pericardial and

particularly valvular), and retroperitoneal inflammatory-fibrotic pathology. The non-ergolinics, pramipexole and ropinirole, are generally well tolerated.

Sponsor's Rationale for Treatment with Rotigotine

The currently marketed non-ergolinic dopamine agonists pramipexole and ropinirole are relatively short-acting, and, consequently, patients take multiple oral doses throughout the day. Oral dopamineric agonists approved for Parkinson's disease in various markets have generally not yielded ideal, stable 24-hour blood levels. The daily "peak and trough" blood levels produced by multiple daily doses of an oral agonist result in a fluctuating stimulation of the dopaminergic neurons. This fluctuation may contribute to the pathogenesis of the motor complications in Parkinson's disease. Preclinical studies and clinical trials using continuous intravenous or subcutaneous drug administration support this hypothesis, but these routes of administration are not practical for daily routine clinical use. To date, only limited methods of chronic, 24-hour drug delivery of a dopaminergic agonist are available and none is approved in the U.S. One is the invasive treatment with subcutaneous apomorphine pumps, which is inconvenient for patients. The other option is the use of the ergolinic compound cabergoline; however, both compounds are only available in a limited number of countries and have the disadvantage of possible ergolinic side effects. Subcutaneous prn injection of apomorphine, a dopaminergic agonist, is also used throughout the world (including the U.S.) as treatment for acute "rescue" for "off" periods

Rotigotine is a non-ergolinic $D_3/D_2/D_1$ dopamine agonist. Although the sponsor proposes that the therapeutic benefit of rotigotine occurs via the simultaneous activation of the D_3, D_2, and D_1 receptors of the caudate-putamen in the brain, the precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown. The sponsor notes that this simultaneous activation of receptors is considered to have advantages over the activation of individual dopamine receptors with the modulatory role of the D_3 receptor being demonstrated in a recent review. Rotigotine has a high in vitro affinity at all dopamine receptor subtypes which is particularly high at the D_3 receptor (K_i 0.71nM), about 10-fold less at the D_2, (i.e. less potent), and about 100-fold less at the D_1 receptor. Rotigotine also has high intrinsic (agonistic) activity on all dopamine receptor subtypes which, again, is particularly high for the D_3 subtype. The very high in vitro activity is reflected in a very high in vivo efficacy with an estimated minimum effective dose of 10µg/kg in MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-hemilesioned monkeys. There is also evidence that rotigotine has antagonistic activity at α_2 adrenergic receptors. Considering that activation of α_2 adrenergic receptors (e.g. as occurs with clonidine treatment) lowers blood pressure, presumably by inhibiting adrenergic activation via activation of presynaptic α_2 adrenergic receptors that inhibit adrenergic output, it is conceivable that this pharmacological activity could result in increased blood pressure.

Rotigotine effectively improved motor deficits and disability in animal models of Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered transdermally. Rotigotine is intended to be administered continuously using a transdermal delivery system. Once daily application of Neupro produces relatively continuous rotigotine plasma levels. In animal models of Parkinson's disease the presence of continuous plasma levels

of dopamine agonists, including rotigotine, resulted in a lower incidence of dyskinesias compared to pulsatile plasma levels produced by intermittent administration.

The sponsor considers that rotigotine is an ideal candidate for delivery via a transdermal patch. A transdermal delivery system provides a vehicle to non-invasively administer a dopamine agonist like rotigotine in a more continuous fashion. Schwarz Biosciences, Inc. and Schwarz Biosciences GmbH, affiliates of Schwarz Pharma, have undertaken the development of rotigotine (a new chemical entity) in the United States (U.S.) and Europe to provide sustained drug delivery that may provide more continuous plasma concentrations of a dopaminergic agonist (compared to orally administered drugs) with once daily dosing for the treatment of patients with early [redacted] This NDA is the first submission requesting marketing authorization in any country for any indication with rotigotine.

2.3 Availability of Proposed Active Ingredient in the United States

Rotigotine has recently (2/06) been approved by EMEA for treatment of early Parkinson's Disease. Responder analyses were the primary statistical analyses for the primary efficacy endpoint for EMEA instead of the change from baseline that was the primary statistical analysis for the Agency.

2.4 Important Issues With Pharmacologically Related Products

Issues of significant concern, particularly for safety, for dopaminergic agonists (and essentially all drug increasing dopaminergic tone) include hypotension/orthostatic hypotension, falls, dizziness/light-headedness, nausea/vomiting, somnolence/sleep attacks, melanoma, retinal toxicity (particularly based upon animal toxicology results), pathological gambling, and hypersexuality.

2.5 Presubmission Regulatory Activity

Presubmission discussion between the Agency and the sponsor dealt with the need to address the potential for rotigotine to produce classical effects of dopaminergic agonists. The DNDP drew particular attention to the issues of sleep attacks and the sponsor's need to address (exclude or at least characterize) the possibility of rotigotine-induced QTc prolongation by adequately assessing this issue in an appropriate study. Furthermore, the DNDP advised the sponsor at the pre-NDA meeting on particular issues including DNDP's desire to : 1) conduct separate safety analyses for the pools of patients included in the pivotal studies, the placebo-controlled studies, and primarily for open-label studies; 2) present exposure data by showing a breakdown by gender, dose, and duration of treatment (e.g. # males exposed for a certain time at a certain dose; # females exposed for a certain time at a certain dose); 3) submit analyses of efficacy data of completers at 3 months for the pivotal trials; 4) submit analyses of data separately for patients

with early vs advanced Parkinson's Disease; 5) submit analyses of safety data according to the dose at the time of the safety data collection; 6) submit analyses of treatment-emergent adverse events (TEAEs) for a host of various AE terms possibly suggestive of falls, for a host of various AE terms possibly suggestive of hypotension/orthostatic hypotension/dizziness/light-headedness, and for a host of various AE terms possibly suggestive of sleep attacks; 7) present analyses of laboratory results, vital signs, and ECGs (especially QTc) according to procedures specifically outlined in the pre-NDA meeting minutes; 8) see particularly PK and safety analyses; 9) review safety data (e.g. orthostatic VS and 12 lead ECGs) collected at various times (over 24 hours) after patch application at PK steady state for the highest daily rotigotine doses (e.g. 13.5, 18 mg); 10) review appropriate QTc data/analyses because DNDP thought that there were important shortcomings in the availability of QTc data (derived from standard 12 lead ECGs) to assess the potential effect of rotigotine for prolonging QTc at various times over 24 hours after patch application at high daily doses of rotigotine (e.g. 13.5 — ,) at PK steady state; and 11) review supplementary, less detailed safety analyses of various populations treated with transdermal rotigotine (advanced Parkinson's disease patients, RLS patients, healthy subjects).

2.6 Other Relevant Background Information

There is no other relevant background information worthy of discussion here

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

I have no significant comments to make here and refer to the primary CMC review by Dr. T. Broadbent.

3.2 Animal Pharmacology/Toxicology

I have no significant comments to make here and refer to the pharmacology/toxicology review by Dr. P. Roney.

3.3 Biopharmaceutics

I have no significant comments to make here and refer to the clinical pharmacology/biopharmaceutical review by Dr. R. Kavanagh.

3.4 Statistics

I have no significant comments to make here and refer to the statistical review by Dr. O. Siddiqui.

Dr. Siddiqui agreed with my review that the sponsor clearly demonstrated the efficacy of rotigotine for treatment of early Parkinson's Disease.

3.5 Division of Scientific Investigations

I have no significant comments to make here and refer to the review by Dr. N. Khin.

3.6 Clinical Safety Review

I have no significant comments to make here and refer to the team safety review by Drs. G. Boehm, M. Stone, and A. Hughes. The Executive Summary from this review is presented in section 1.3.3 (Summary of Clinical Findings : Safety).

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The various studies were conducted in North America (U.S. and Canada) and many other countries throughout the world. I have specified the countries in which the main studies contributing to the demonstration of efficacy were conducted in section 6.1.3.

4.2 Tables of Clinical Studies

Completed, Phase 2 Dose-Ranging Trials of Rotigotine in Early-Stage, Idiopathic Parkinson's Disease

Trial Number/Clinical Development Phase/Trial Design	# Subjects Receiving Rotigotine	# Subjects Receiving Placebo	Maximum Treatment Duration
SP534 (Part 1)/Phase 2a/SC, DB, PC, parallel-group, fixed-dose, dose-ranging in early-stage, Parkinson's disease; cohorts of 9.0mg and 13.5mg daily doses.	10	2	28 days
SP534 (Part 2)/Phase 2a/ SC, DB, PC, parallel-group, dose-titration, dose-ranging in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	10	2	28 days
SP540/Phase 2a/MC, SB[a], dose-titration, efficacy, safety in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	31	0	28 days
SP535/Phase 2a/SC, DB, PC, dose-escalation, safety and tolerability in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	8	2	28 days
SP506/Phase 2b/MC, DB, PC, parallel-group, dose-ranging in early-stage Parkinson's disease subjects; 4.5mg, 9.0mg, 13.5mg, and 18.0mg daily doses.	253[b]	76[b]	3 months
Total	312	82	-

DB=double-blind, MC=multicenter, PC=placebo-controlled, SB=single-blind, SC=single center.
a The protocol for SP540 refers to the trial as a single-blind trial, however, the subjects were blinded only to dose; subjects were aware that they were receiving rotigotine.
b In the SP506 CTR, 248 subjects were included in the rotigotine treatment group and 81 in the placebo group for "as treated" analyses. Upon review of the data for pooling, 5 subjects from SP506 were reassigned from placebo to rotigotine to more accurately reflect the subjects' treatment.

Completed, Phase 3 Pivotal Trials in Early-Stage, Idiopathic Parkinson's Disease

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

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

4.3 Review Strategy

My review focused on assessing the efficacy of 3 randomized, double-blind, placebo-controlled study (506, 512, 513) that ranged from treatment for approximately 3 – 9 months.

4.4 Data Quality and Integrity

I do not have any significant concerns about the quality and integrity of the efficacy data in this NDA.

4.5 Compliance with Good Clinical Practices

The sponsor appeared to comply with Good Clinical Practices.

4.6 Financial Disclosures

I reviewed the financial disclosures and do not have any significant concerns with regard to financial disclosures.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

The following summary is abstracted from information provided by the sponsor. The reader is referred to the clinical pharmacology/biopharmaceutical review by Dr. R. Kavanagh for additional details.

Mechanism of Action of Rotigotine

Rotigotine is a non-ergolinic $D_3/D_2/D_1$ dopamine agonist for the treatment of Parkinson's disease. The precise mechanism of action of rotigotine as a treatment for Parkinson's disease is unknown although it is thought to be from simultaneous activation of the D_3, D_2, and D_1 receptors of the caudate-putamen in the brain. This simultaneous activation of receptors is considered to have advantages over the activation of individual dopamine receptors with the modulatory role of the D_3 receptor being demonstrated in a recent review. Rotigotine effectively improved motor deficits and disability in animal models of Parkinson's disease (6-OHDA in rat and MPTP model in monkey) including when administered transdermally. Rotigotine is intended to be administered continuously using a transdermal delivery system.

Once daily application of Neupro produces continuous rotigotine plasma levels. In animal models of Parkinson's disease the presence of continuous plasma levels of dopamine agonists,

including rotigotine, resulted in a lower incidence of dyskinesias compared to pulsatile plasma levels produced by intermittent administration.

Absorption

Following application, rotigotine is continuously released from the transdermal system to the skin. Approximately 45% of the drug content of the transdermal system is released within 24 hours. Steady-state rotigotine plasma concentrations are reached after one to two days of transdermal system application and are maintained by once daily application in which the system is worn for 24 hours.

In the clinical trials of rotigotine effectiveness, the transdermal system application site was rotated from day to day (abdomen, thigh, hip, flank, shoulder, or upper arm) and the mean trough plasma concentrations of rotigotine were stable over the six months of maintenance treatment.

The bioavailability of rotigotine was similar across all application sites.
Because rotigotine is administered transdermally, food will not affect absorption, and the product may be administered without regard to the timing of meals.

Pharmacokinetic Parameters

Rotigotine displays a dose-proportional pharmacokinetic profile over a daily dose range of 2 mg/24 hrs to 8 mg/24 hrs. Similar pharmacokinetics were observed in patients with Parkinson's disease and healthy subjects.
Exposure to rotigotine from daily application of Neupro in healthy subjects and Parkinson's disease patients exhibit a consistent exposure profile. Repeated daily administration resulted in stable plasma levels. After removal of the patch, plasma levels decrease with an elimination half-life of 5 to 7 hours.
Pharmacokinetic parameters observed after single dose or multiple dose application of 10 cm^2 (2 mg/24 hrs) to 40 cm^2 (8 mg/24 hrs) Neupro to healthy subjects are summarized in Table 2.

Table 2 Steady-State Rotigotine Pharmacokinetic Parameters for System Applied to Ventrolateral Abdomen

Dose/24 hrs (Size) (n)	Study/ Design	Cmax[1] (ng/mL)	AUC(0-t)[1] (ng/mL*h)	CL[1] (L/min)
4.5 mg/24 hrs ($10cm^2$) (n=29)	503 MD[3]	0.31 ± 0.17[2]	6.1 ± 2.8[2]	8.1 ± 5.3[2]
9 mg/24 hrs ($20cm^2$) (n=13)	502 SD[4]	0.56 ± 0.19	11.1 ± 4.1	8.0 ± 2.2
18 mg/24 hrs ($40 cm^2$) (n=11)	502 SD[4]	1.19 ± 0.35	23.7 ± 8.5	7.5 ± 2.0

[1]Mean ± standard deviation
[2]Last day of administration
[3]MD = Multiple dose
[4]SD = Single dose

Distribution

Rotigotine is widely distributed in the body. The weight normalized apparent volume of distribution in humans is approximately 84 L/kg after repeated dose administration.
The *in vitro* binding of rotigotine to human plasma proteins is approximately 92%, which is mainly mediated by albumin.
The median percentage of unbound fraction in human plasma determined *in vivo* was 10.5%.

Metabolism and Elimination

Rotigotine is extensively metabolized by conjugation and N-dealkylation. In human plasma the predominant metabolites are sulfate conjugates of rotigotine, glucuronide conjugates of rotigotine, and sulfate conjugates of the N-desthienyl- and N-despropyl-metabolites. Rotigotine is primarily excreted in urine (~71%) as inactive conjugates of the parent compound and N-desalkyl metabolites. A smaller proportion is excreted in feces (~23%). The major metabolites found in urine were the sulfate conjugate of rotigotine (16-22% of administered dose), the sulfate conjugate of the N-despropyl metabolite (14-20%), the sulfate conjugate of the N-desthienylethyl metabolite (10-18%) and glucuronide conjugate of rotigotine (11-15%). A small amount of unconjugated rotigotine is renally eliminated (0.06% of the apparent dose).

Pharmacokinetics in Special Populations

Because therapy with Neupro is initiated at a low dose and gradually titrated according to clinical tolerability to obtain the optimum therapeutic effect, adjustment of the dose based on gender, weight, or age is not necessary.

Hepatic Insufficiency

The effect of impaired hepatic function on the pharmacokinetics of rotigotine has been studied in subjects with moderate impairment of hepatic function (Child Pugh classification – Grade B). No dose adjustment is necessary in subjects with moderate impairment of hepatic function. No information is available on subjects with severe impairment of hepatic function. (See **PRECAUTIONS, Hepatic Insufficiency)**

Renal Insufficiency

The effect of renal function on rotigotine pharmacokinetics has been studied in subjects with mild to severe impairment of renal function including subjects requiring dialysis compared to healthy subjects. No dose adjustment is recommended for patients with different stages of impaired renal function.

Gender

Female and male subjects and patients had similar plasma concentrations (body weight normalized) and clearance of rotigotine.

Geriatric Patients

Plasma concentrations of rotigotine are similar in patients above 65 years of age compared to younger patients.

Pediatric Patients

The pharmacokinetics of rotigotine in subjects below the age of 18 years has not been established.

Race

The pharmacokinetic profile in different ethnic groups was similar (White [Caucasian], Black [African descent], and Japanese). No dose adjustment is necessary based on ethnicity.

5.2 Pharmacodynamics

Rotigotine by virtue of its dopaminergic agonistic effects decreases serum prolactin.

The efficacy of rotigotine's dopaminergic stimulation in producing therapeutic benefit in the treatment of early Parkinson's Disease was demonstrated in pivotal, randomized, double-blinded, placebo-controlled trials

5.3 Exposure-Response Relationships

The 506 Study was critical, and most important in establishing exposure-response relationships. The study employed a design in which patients with early Parkinson's Disease were randomized to placebo or one of several (4.5, 9, 13.5, or 18 mg) of rotigotine. Although the mild-moderate numerical benefit/improvement associated with the lowest dose was not statistically significant, benefit/improvement associated with the three higher dose was statistically significant. There did not appear to be any additional therapeutic benefit of the 18 mg dose compared to the 13.5 mg dose.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The sponsor has proposed rotigotine for the signs and symptoms of early-stage idiopathic Parkinson's Disease.

6.1.1 Methods

The efficacy review is based upon 3 "large" randomized, double-blinded, placebo-controlled mutlicenter trials. Although the sponsor considered studies 512 (also referred to as SP512) and 513 (also referred to as SP512) to be pivotal trials and study 506 (also referred to as SP506) to be a supportive trial, I essentially consider all 3 to be pivotal trials. Studies 512 and 513 were flexible dose (4.5, 9, 13.5, or 18 mg daily rotigotine) trials of approximately 6 and 9 months duration respectively and study 506 in which patients were randomized to placebo or one of several fixed rotigotine doses (4.5, 9. 13.5, 18 mg daily) was conducted over nearly 3 months. Technically, study 506 in which the primary efficacy data were collected over a period up to 11 weeks was slightly shorter than the typical minimal duration ("3 months" or 12 weeks) that we ordinarily require for a "pivotal" study. Study 512 was conducted in North America (U.S. and Canada) and study 513 was conducted in Europe (including central and eastern), Australia/new Zealand, Isarael, and Africa and also included an active comparator treatment arm of a dopaminergic agonist, ropinirole, approved in the U.S. and many countries globally. The following general sections include specific study information from each of these studies.

These 3 studies were formally labeled as part I to indicate the randomized, double-blind, placebo-controlled phase and part II to indicate the open-label extension phases. However, because efficacy is assessed solely based upon results of the controlled phase (part I), I will not label or refer to these 3 studies as being related to part I in my presentations and discussions in the efficacy sections.

6.1.2 General Discussion of Endpoints

The primary efficacy endpoint in all 3 studies was the change of UPDRS part II (Activities of Daily Living-ADL subscale) plus part III (motor subscale) from baseline to the end of the study. This is a reasonable primary efficacy endpoint for early Parkinson's Disease. This change from baseline in this combined endpoint or the change in the part III motor subscale is commonly used in studies of Parkinson's Disease. The ADL subscale (Table 1) consists of scoring 13 elements involved in daily activities from 0 – 4 (i.e. 0, 1, 2, 3, or 4 with 0 for normal and 4 for greatest severity of dysfunction). The motor subscale (Table 2) involves scoring 14 elements of motor function from 0 – 4 (i.e. 0, 1, 2, 3, or 4 with 0 for normal and 4 for greatest severity of dysfunction).

Considering that the experimental drug under study is a dopaminergic agonist and that a greater therapeutic effect might be expected on part III from a dopaminergic agonist than on combined parts II plus III, one might expect that the magnitude of therapeutic effect on the combined primary efficacy endpoint might be less than the effect on the motor subscale alone.

Study 506

In study 506, secondary efficacy endpoints included : 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) alone; 2) changes in the sum of parts I + II + III from baseline to the end of study; and 3) change in Hoehn and Yahr category from baseline to the end of the study. Other efficacy endpoints were : 1) the % of two categories of "responders" (i.e. $\geq$ 20 % decrease of sum of motor and ADL scores and $\geq$ 30 % decrease of sum of motor and ADL) based upon the change from baseline to the end of the study; 2) the relative (i.e. %) change from baseline in the sum of the motor and ADL scores of the UPDRS from baseline to the end of the study; and 3) the change of the sum of motor and ADL scores from baseline to visits (e.g. visit 4/4 weeks and visit 5/7 weeks) during the study.

Studies 512 and 513

In studies 512 and 513, the secondary efficacy measures were : 1) relative (i.e. %) 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. Other efficacy endpoints included : 1) the change in Hoehn and Yahr category from baseline to the end of the study; and 2) the change in Clinical Global Impression (CGI) from baseline to the end of the study.

Many of these secondary efficacy endpoints are often evaluated as secondary efficacy endpoints in studies of Parkinson's Disease and the change in motor score alone is occasionally a primary

Table 1 UPDRS Part II Activities of Daily Living (ADL)

II. ACTIVITIES OF DAILY LIVING (for both "on" and "off")

5. Speech
0 = Normal.
1 = Mildly affected. No difficulty being understood.
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6. Salivation
0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooli
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7. Swallowing
0 = Normal.
1 = Rare choking.
2 = Occasional choking.
3 = Requires soft food.
4 = Requires NG tube or gastrotomy feeding.

8. Handwriting
0 = Normal.
1 = Slightly slow or small.
2 = Moderately slow or small; all words are legible.
3 = Severely affected; not all words are legible.
4 = The majority of words are not legible.

9. Cutting food and handling utensils
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can cut most foods, although clumsy and slow; some help needed.
3 = Food must be cut by someone, but can still feed slowly.
4 = Needs to be fed.

10. Dressing
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Occasional assistance with buttoning, getting arms in sleeves.
3 = Considerable help required, but can do some things alone.
4 = Helpless.

11. Hygiene
0 = Normal.
1 = Somewhat slow, but no help needed.
2 = Needs help to shower or bathe; or very slow in hygienic care.
3 = Requires assistance for washing, brushing teeth, combing hair, going to bathroom
4 = Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bed clothes
0 = Normal.
1 = Somewhat slow and clumsy, but no help needed.
2 = Can turn alone or adjust sheets, but with great difficulty.
3 = Can initiate, but not turn or adjust sheets alone.
4 = Helpless.

13. Falling (unrelated to freezing)
0 = None.
1 = Rare falling.
2 = Occasionally falls, less than once per day.
3 = Falls an average of once daily.
4 = Falls more than once daily.

14. Freezing when walking
0 = None.
1 = Rare freezing when walking; may have starthesitation.
2 = Occasional freezing when walking.
3 = Frequent freezing. Occasionally falls from freezing.
4 = Frequent falls from freezing.

15. Walking
0 = Normal.
1 = Mild difficulty. May not swing arms or may tend to drag leg.
2 = Moderate difficulty, but requires little or no assistance.
3 = Severe disturbance of walking, requiring assistance.
4 = Cannot walk at all, even with assistance.

16. Tremor (Symptomatic complaint of tremor in any part of body.)
0 = Absent.
1 = Slight and infrequently present.
2 = Moderate; bothersome to patient.
3 = Severe; interferes with many activities.
4 = Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism
0 = None.
1 = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.