QT increased

SP512DB/Subject 14102/84102, a 68 year old white male with Parkinson's disease, prostatic hypertrophy, daytime sleepiness, atrial fibrillation, and osteoarthritis had a QTcB increase of > 60msec compared to baseline The subject discontinued from the study for this finding. The following table summarizes the subject's QTcB values.

Visit	Date	QTcB Value (msec)	Rotigotine Dose	
1 (Screening)	04 Jun 2002	382	0 2 (Baseline)	
	20 Jun 2002	406, 396, 403 (mean: 402)	0	
4	24 Jul 2002	380	13.5	
5	31 Jul 2002	393	13.5	
8	25 Oct 2002	395	13.5	11/Open Label
17 Jan 2003 Visit 1[a]	472	13.5		

a Visit 11 of Part 1 of the SP512 protocol coincided with Visit 1 of Part 2 (the open-label extension) of this protocol.

The sponsor reported that an additional ECG from 1/17/03 had a QTc of 545msec. The subject underwent a pacemaker insertion. The event was reported as resolved.

SP533/Subject 205/605, A 71 year old Caucasian male with Parkinson's disease, RBBB, left axis deviation, probable Lev's disease, and anxiety disorder had an SAE of QTcB prolonged. The subject's screening ECG showed sinus rhythm, bifasicular block (RBBB, LAHB), and mildly prolonged QTcB. His two baseline QTcB results were 406 and 418msec. The subject's first rotigotine patch (dose 9mg) was 8/9/99. On 8/18/99, his first day of rotigotine 27mg, he had a QTcB of 489msec. On an ECG the next day his QTcB was 476msec. The rotigotine patches were removed and he was withdrawn from the trial. The narrative reported that of the 20 post treatment ECGs, only 1 had a QTcB>470msec (QTcB 487msec 4 days after stopping rotigotine). The ECGs were re-measured by Cardiac Alert, a central reader, and an NIH cardiologist and the sponsor reported that none of the subject's QTcB values were >470msec (protocol criteria for discontinuation from the study). The highest on treatment QTcB reported by Cardiac alert was 433msec.

The following paragraphs summarize infrequently occurring SAEs of potential concern. The relationship between these events and rotigotine is uncertain.

Rash erythematous

SP513DB/Subject 101203/801203, a 77 year old white male with Parkinson's disease, hypertension, atrial fibrillation, and an enlarged prostate was receiving rotigotine 18mg for 10 days (total duration of rotigotine 32 days) when he experienced a diffuse "exanthema and enanthema" requiring hospitalization. Trial medication was stopped and he was treated with IV hydrocortisone, dithiaden (antihistamine), and topical zinc oil. The event resolved. Concomitant medications included furosemide, acetylsalicylic acid, digoxin, omnic, selegiline, and amantidine.

Convulsions

SP506/Subject 23008/0707 a 74 year old Asian male with Parkinson's disease, diabetes mellitus, and hypertension experienced a witnessed generalized tonic-clonic seizure lasting about 15 minutes followed by post ictal confusion for 30 minutes. He sustained a laceration on his forehead when he fell during the event. Blood glucose immediately following the event was 160mg/dL. He was taken to an ED and treated with diazepam and phenobarbital. Brain CT showed diffuse cerebral atrophy with no lacunar lesions and no mass effect. His blood urea, creatinine, and electrolytes were reportedly normal. An EEG performed several weeks after the event showed "a poor alpha index. Background activity consisted of fast beta activity that was thought likely to be induced by phenobarbital. No paroxysmal activity was noted, while resting or with activation (hyperventilation, photic stimulation)." Concomitant medications were amantadine 100mg 3 times daily, aspirin 150mg once daily, metformin 500mg twice daily, atenolol 50mg daily, amlodipine 5mg once daily, inderal 40mg 3 times daily, beta-carotene 1 tablet twice daily for 3 days, calcium carbonate 750mg twice daily for 3 days. Loratadine 10mg daily and topical betamethasone and ketoconazole twice daily were added during the trial.

Syncope

SP506/Subject 01101/1151, a 52 year old female with Parkinson's disease, hypothyroidism, irritable bowel syndrome, and dust and mold allergies, experienced loss of consciousness while driving. The subject had been receiving rotigotine 18mg for 32 days when she blacked out while driving and went off the road. She was aroused when the car hit gravel. Earlier in the study she experienced dizziness and her blood pressures were 120/70 sitting and 110/70 standing. She was discontinued from the trial for this event and was reportedly completely recovered one week later.

SP512OL/Subject 10406/80406, a 72 year old white female with Parkinson's disease, cataracts, depression, fluctuating blood pressure, and other medical problems, experienced a syncopal episode. The subject had been receiving rotigotine 13.5mg for 167 days when after awakening in the afternoon she felt nauseated. She arose to go to the bathroom and felt as if the room were spinning. She then fainted and fractured her humerus when she fell. An ECG demonstrated sinus rhythm and a right ventricular conduction delay. Her blood pressure was described as somewhat low (actual value not available). She continued in the trial.

SP513OL/Subject 103720/803717 a 56 year old white male with Parkinson's disease, sinusitis, constipation, inguinal hernias, hypertension and myopia had a syncopal episode 20 days after the start of open label rotigotine. While sitting on the toilet, the subject became dizzy and had right sided chest pain lasting a few minutes. The narrative did not report loss of consciousness. He was hospitalized and ECG and blood work (including cardiac enzymes and D-dimer) were normal. He was discharged the same day. The subject continued in the trial. Concomitant medications were atenolol, cilazapril, and selegiline.

Psychosis

SP513OL/Subject 101311/801309, a 73 year old white male with Parkinson's disease, and hypertension, experienced visual hallucinations 6 days after starting open label rotigotine. His rotigotine dose was 4.5mg at the time of the event. During the preceding DB trial, he received rotigotine (highest dose 13.5mg, modal dose 9mg). His wife found him confused, restless, walking about the house, having problems communicating, and having tendency to fall. The subject complained of vertigo and leg pain. On examination in the hospital he was oriented to basic information, but he was not answering questions and he was falling asleep during the examination. Physical examination, spinal x-ray, brain CT, and blood tests were unremarkable. The subject was diagnosed with psychosis following a psychiatric examination and was treated with tiapridal, and risperidone. Concomitant medications at the onset of the SAE were nitrendipine, selegiline, piracetamum, acetylsalicylic acid and pentoxyphyllinum. The SAE was reported as resolved.

Hallucinations

SP591/ Subject 10/1007 This 68 year old black male with Parkinson's disease, bilateral pulmonary emboli and s/p TURP, experienced hallucinations approximately one month after starting rotigotine and six days after an increase in dose to 54mg. The hallucinations were described only as mild and lasting 9 hours. Nineteen days later, the subject experienced a second episode of hallucinations described as moderate intensity. These were visual hallucinations and the narrative noted that the hallucinations precluded normal activity. Trial medication and L-dopa were decreased at this time without improvement. The subject was then admitted to a neurology unit and started on donepezil. The subject was discontinued from the trial and the event was reported as completely resolved. Concomitant medications at the time of the onset of this event were levodopa/benserazide, trandolapril, aspirin, glyceryl trinitrate, bendrofluazide, sterculia, lactulose, quinine, nortriptyline, peppermint oil, ipratropium bromide, and glycerol suppository.

SP513 (Part II)/Subject 103307/803307, a 55 year old male with a history of depressive mood, inguinal hernia, retinopathy, hypertension, nephrolithiasis and Parkinson's disease was hospitalized for nephrolithiasis and percutaneous nephrolithectomy and experienced hallucinations. Following nephrolithectomy the subject experienced visual hallucinations that disappeared spontaneously. Approximately 4 months later, the subject experienced hallucinations one day after increasing rotigotine dose from 13.5mg/day to 18mg/day. He hallucinated that his wife was talking to strange men and he saw the face of his friend at night. He accused his wife of being unfaithful and accused friends of bothering his wife. The rotigotine dose was reduced to 13.5mg/day but the hallucinations continued. The rotigotine was stopped and the subject was started on quetiapine. The hallucinations resolved. Concomitant medications at the time of the onset of hallucinations were selegiline, tolperisone, telmisartan, metixene, and bisoprolol.

Hallucination/ Postural Hypotension

SP512OL/Subject 10407/80407 a 67 year old white female with Parkinson's disease, chest pain, knee pain, anxiety, low blood pressure, and other medical problems, first experienced postural hypotension and hallucinations 188 days after starting rotigotine. She was found lying on the floor at home and could not recall what happened. During a 2 day hospitalization, she was noted to have a postural decrease in systolic blood pressure from 134 (lying) to 118mm HG (sitting). During the hospitalization she experienced hallucinations that were attributed to the amantadine she was taking. Amantadine was stopped and cardidopa/levodopa was started. Her ECG showed sinus rhythm and her only identified lab abnormality was an elevated CPK (in the 800s attributed to hemolysis). She was discharged and approximately 2 and ½ months later she fell again and continued to experienced hallucinations (she stated she was pushed by a ghost). Postural hypotension was not mentioned at the time of this event. She continued in the trial.

Hypotension Postural

SP512OL/Subject 13806/83805, a 71 year old white female with Parkinson's disease, stress incontinence, cataracts, celiac disease, and other medical problems, discontinued from a trial for postural hypotension. The subject had a supine BP after 5 min rest of 144/62, after 1 min standing 120/64, and after 3 min standing 130/70. The narrative did not report any symptoms associated with this finding.

SP513OL/Subject 100505/800505, a 64 year old white female with a history of Parkinson's disease, cervical myelopathy, osteochondrosis, protein allergy, poliomyelitis, and other medical problems experienced dizziness 99 days after the start of open label rotigotine. She was hospitalized the next day for worsening Parkinson's symptoms. Her dizziness was related to standing and walking and she had a supine BP of 120/80 and a standing BP (3 min later) of 90/60 that was associated with dizziness. During her hospitalization, trial medication was stopped and levodopa was started. Her Parkinson's symptoms improved and her orthostatic hypotension resolved.

Hepatic enzymes increased

SP513OL/Subject 105604/805604 a 42 year old white female with a history of Parkinson's disease, mood swings, hypertension, and urinary dribbling experienced increased hepatic enzymes 21 days after starting open label rotigotine. This subject received rotigotine during the preceding double blind controlled trial (maximum dose 13.5mg, modal dose 9mg).The following table summarizes hepatic enzyme results for this subject.

Date (double-blind)	**GGT (U/L)**	**AST (U/L)**	**ALT (U/L)**	**AP(U/L) SP513 Part I**
30 Apr 2002	75	21	30	94 (Screening) 25
May 2002	97	30	44	93 (Baseline) 31
Aug 2002	57	21	32	74 23 Nov 2002
	84	26	42	102 15 Feb 2003
	70	26	46	120
SP513 Part II (open-label)				
19 Mar 2003	151	39	81	154 12 Apr 2003
	267	62	159	283 15 Apr 2003
	142	40	84	-
17 May 2003	58	34	47	91 (Safety Follow-Up)

Note: GGT=gamma-glutamyl transpeptidase, AST=aspartate aminotransferase, ALT=alanine aminotransferase, and AP=alkaline phosphatase.
Note: Reference ranges for the liver enzymes were GGT: 0 to 45U/L, AST: 0 to 42U/L, ALT: 0 to 48U/L, and AP: 20 to 125U/L.

On 3/19/03 her total bilirubin was 0.5mg/dL. The CRF included no other on treatment liver related lab results. The subject was hospitalized on — increased hepatic enzymes and was discontinued from the trial at that time. She was discharged on — ıth the diagnosis of cholelithiasis, diabetes mellitus, arthritis, and hypertension. This subject was taking no other medications at the time of the onset of this SAE.

SP512 (Part II)/Subject 10201/80202, a 50 year old male with a history of headaches, hypercholesterolemia, tachycardia, hypertension, back pain, depression, colon polyps, hernia repair, Parkinson's disease, and other medical problems experienced elevated hepatic enzymes. At the time of the event, the subject was taking rotigotine 13.5mg/day and had been on this dose for 349 days. The subject experienced RUQ pain, jaundice, and elevated transaminases that were felt due to passage of gall stones or biliary sludge. The subject's liver related lab tests are provided below:

	AST Ref Range 0-42U/L	ALT Ref Range 0-48U/L	Alkaline phosphatase Ref Range 20-125U/L	Total bilirubin Ref Range 0-1.278mg/dL
End Titration (1/02/03)	22	27	46	1
Month 6	25	31	60	0
Month 12	459	319	141	5
Prior to 1/20/04	690	604	130	4.8
Month 18	19	23	52	8

In addition, the subject had negative results for P-ANCA, anti-LKM, AMA, ASMA, HbSAg, and anti-HCV. Alpha-1 anti-trypsin was 182mg/dL and ceruloplasmin was 33mg/dL. The subject underwent laproscopic cholecystectomy on — and the surgeon noted the liver appeared normal without micronodular or macronodular pattern. The liver biopsy showed no signs of hepatitis. Trial medication was continued throughout the event. Concomitant medications included aspirin, amantadine, ascorbic acid, atenolol, carbidopa/levodopa, cyclobenzaprine, selenium, and tocopherol.

Rhabdomyolysis

650 (Part II)/ Subject 13011, an 80 year old female with a history of arthritis, colonic and gastric polyps, cataracts, diabetes mellitus, diabetic neuropathy, hypertension, hypercholesterolemia, Parkinson's disease and other medical problems experienced rhabdomyolysis. One hundred and sixty days after the start of open label rotigotine, she developed extreme weakness and was unable to arise from a seated position. She remained on the floor for 14 hours, unable to rise, asleep most of the time. She was found by a family member and brought to a hospital. She complained of diffuse muscle aches and had a CK of 10,099U/L and myoglobinuria. The narrative did not mention elevated temperature, increased muscle rigidity, or autonomic instability. She was diagnosed with rhabdomyolysis secondary the 14 hours she spent on the floor. She was treated with iv fluids and bicarbonate; rotigotine was held for 2 days. She was also treated with levofloxacin for a urinary tract infection. She improved and was discharged. She continued rotigotine for approximately 2 weeks and then underwent dose de-escalation due to foot swelling that had preceded the hospitalization for rhabdomyolysis.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

Schwartz summarized the reasons for discontinuation from early Parkinson's disease clinical trials. They note that more than one reason for discontinuation could be recorded for a particular subject.

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

For the early stage Parkinson's disease controlled and open label trials (pool S3), 23% (247/1093) of rotigotine subjects discontinued prematurely (Safety Update, p.29). Adverse event was the most common reason for discontinuation (15%, 159/1093)[3] followed by lack of efficacy (4%, 48/1093),

[3] In the section addressing reasons for discontinuation, Schwartz reported that the most common reason for discontinuation from pool S3 trials was adverse event (15%, 159/1093), yet in the section on discontinuation for adverse events, Schwartz reported that 16% (173/1093) of subjects discontinued from pool S3 trials for AEs. When asked about this apparent discrepancy, Schwartz replied that the difference was primarily due to discrepancies between Trial Termination sheets (reason for termination field) of the CRFs and AE CRF pages (outcome of AE field). Schwartz either did not resolve the discrepancies or did not receive responses to queries of investigators about discrepancies. In three

subject withdrew consent (4%, 42/1093), other (0.6%, 7/1093), unsatisfactory compliance (0.4%, 4/1093), protocol violation (0.3%, 3/1093), and lost to follow up (0.2%, 2/1093).

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

In the NDA, Schwarz reported that for the pooled early stage Parkinson's disease controlled trials, the percentage of subjects prematurely discontinuing was similar for all three treatments. Adverse event and lack of efficacy were the most common reasons for discontinuation. A higher percentage of rotigotine and ropinirole subjects discontinued for adverse event than placebo subjects. The following table summarizes the reasons for discontinuation from early stage Parkinson's disease controlled trials.

Summary of discontinuation – Pool S1

	Placebo N=289	**Rotigotine N=649**	**Ropinirole N=228**
Parameter	**n (%)**	**n (%)**	**n (%)**
Subjects discontinuing	68 (24)	134 (21)	54 (24)
Reasons for discontinuation:			
Protocol violation	2 (1)	3 (1)	1 (<1)
Lack of efficacy	31 (11)	29 (5)	8 (4)
Adverse event	16 (6)	86 (13)	29 (13)
Unsatisfactory compliance of subject	3 (1)	2 (<1)	4 (2)
Subject withdrew consent	14 (5)	26 (4)	15 (7)
Lost to follow-up	2 (1)	1 (<1)	0
Other	10 (4)	4 (1)	3 (1)

NOTE: More than 1 reason for discontinuation may be presented for a subject.
Data source: ISS Table 12.1
From Summary of Clinical Safety, page 51

7.1.3.2 Adverse events associated with dropouts

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

For early stage Parkinson's disease Phase II/III trials, Schwartz reported that 173 subjects discontinued for one or more treatment emergent AEs (Safety Update, table 53.1, pp. 800-7). In the table below, I identify the AEs leading to discontinuation from early Parkinson's Phase II/III disease trials.

Treatment Emergent AEs Leading to Discontinuation from Phase II/III Early Parkinson's Disease Studies

Event leading to discontinuation	% (n)	Event leading to discontinuation	% (n)
Application site reaction	5.2% (57)	Bundle Branch Block	0.2% (2)
Dermatitis contact	0.8% (9)	Arrhythmia	<0.1%(1)
Hypotension postural	0.6% (7)	Extrasystoles	<0.1%(1)

additional cases, Schwartz determined the AEs leading to discontinuation were not treatment emergent. (Response to Reviewer Inquiry, 9/2/05).

Sweating increased	0.4% (4)	Fibrillation atrial	<0.1%(1)
Mouth dry	<0.1%(1)	Tachycardia	<0.1%(1)
Accident NOS	0.2% (2)	Gamma-GT increased	<0.1%(1)
Oedema peripheral*	0.3% (3)	Hepatic enzymes increased	<0.1%(1)
Fatigue	0.2% (2)	Weight decreased	0.2% (2)
Chest pain	<0.1%(1)	Dehydration	<0.1%(1)
Asthenia	<0.1%(1)	Hyperglycemia	<0.1%(1)
Fever	<0.1% (1)	NPN increased	<0.1%(1)
Hyperaesthesia	<0.1% (1)	Oedema periorbital	<0.1%(1)
Malaise	<0.1% (1)	Back pain	0.3% (3)
Oedema dependent*	<0.1% (1)	Muscle weakness	<0.1%(1)
Pain	<0.1% (1)	Myalgia	<0.1%(1)
Rigors	<0.1% (1)	Myocardial infarction	0.2% (2)
Sudden death	<0.1% (1)	Thrombocytopenia	<0.1%(1)
Hypotension	0.4% (4)	Somnolence	1.5% (16)
ECG abnormal	0.3% (3)	Insomnia	0.6% (7)
Syncope	0.2% (2)	Hallucination	0.4% (4)
Oedema dependent*	<0.1% (1)	Depression	0.3% (3)
Hypertension	<0.1% (1)	Paranoid reaction	0.2% (2)
Oedema generalized	<0.1% (1)	Thinking abnormal	0.2% (2)
Oedema peripheral*	<0.1% (1)	Psychosis	<0.1%(1)
Headache	0.6% (7)	Sleep attacks	<0.1%(1)
Confusion	0.4% (4)	Dyspnea	0.2% (2)
Parkinsonism aggravated	0.4% (4)	Pneumonitis	<0.1%(1)
Dizziness	0.3% (3)	Rhinitis	<0.1%(1)
Gait abnormal	0.3% (3)	Fall	<0.1%(1)
Ataxia	0.2% (2)	Surgical Intervention	<0.1%(1)
Hypertonia	0.2% (2)	Dermatitis	0.2% (2)
Vertigo	0.2% (2)	Rash erythematous	0.2% (2)
Hypokinesia	<0.1% (1)	Rash maculo-papular	0.2% (2)
Tremor	<0.1% (1)	Alopecia	<0.1% (1)
Convulsions	<0.1% (1)	Bullous eruption	<0.1% (1)
Neuralgia	<0.1% (1)	Dermatitis contact	<0.1% (1)
Neuropathy	<0.1% (1)	Pruritis	<0.1% (1)
Adrenal insufficiency	<0.1% (1)	Urticaria	<0.1% (1)
Nausea	1.9% (21)	Bladder spasm	<0.1% (1)
Vomiting	1.2% (13)	Urinary incontinence	<0.1% (1)
Constipation	0.3% (3)	Urinary tract infection	<0.1% (1)
Anorexia	<0.1% (1)	Vascular disorder	<0.1% (1)
Abdominal pain	<0.1% (1)	Vision abnormal	<0.1% (1)
QT increased	0.4% (4)	Leucopenia	<0.1% (1)
Palpitation	0.3% (3)		

*Events reported under more than one body system
From Safety Update Table 53.1

Safety Update Table 53.1, that lists the AEs leading to discontinuation, has fewer AEs than table 54.1.2 which listed the AEs leading to discontinuation and ID numbers for subjects who discontinued for AEs. When asked about this discrepancy, Schwartz explained that table 54.1.2 included not only subjects with drug discontinued as the action taken for AE but also subjects that had "not applicable" or missing data, even when Schwartz was aware that these subjects continued

in the trial (9/9/05 submission). Schwartz submitted updated tables that identified only those subjects that discontinued for AEs.

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

In early stage Parkinson's disease controlled trials, 13% (86/649) of rotigotine subjects discontinued for AEs compared to 13% (30/228) of ropinirole subjects and 6% (18/289) of placebo subjects (Summary of Clinical Safety, p.103). The most common AE leading to discontinuation of rotigotine subjects was application site reaction (5.2%, 34/649). In the following table, I summarize the AEs leading to discontinuation of more than one rotigotine subject and more frequently compared to ropinirole or placebo.

Adverse Events Leading to Discontinuation of at Least 2 Rotigotine Subjects and Occurring More Frequently Compared to Placebo or Ropinirole, Early Stage Parkinson's Disease Phase II/III Controlled Trials

Preferred Term	Placebo (n=289)		Rotigotine (n=649)		Ropinirole (n=228)	
	%	N	%	N	%	N
Application site reaction	0	0	5.2%	34	0	0
Nausea	0	0	2%	13	2.6%	6
Vomiting	0	0	1.2%	8	0.9%	2
Insomnia	0	0	0.8%	5	0.4%	1
Somnolence	0	0	0.6%	4	1.3%	3
Headache	0.3%	1	0.5%	3	0	0
QT increased	0.3%	1	0.5%	3	0	0
Palpitation	0	0	0.5%	3	0	0
Hypotension postural	0.3%	1	0.3%	2	0	0
Sweating increased	0	0	0.3%	2	0	0
Fatigue	0	0	0.3%	2	0	0
Oedema peripheral	0	0	0.3%	2	0	0
Hypotension	0.3%	1	0.3%	2	0	0
ECG abnormal	0	0	0.3%	2	0	0
Gait abnormal	0	0	0.3%	2	0	0
Bundle Branch Block	0.3%	1	0.3%	2	0	0
Depression	0	0	0.3%	2	0	0
Rash erythematous	0	0	0.3%	2	0	0
Rash maculo-papular	0	0	0.3%	2	0	0

From ISS table 53.1, pp.2008-2013.

AEs Leading to Discontinuation from Trials for Other Indications

Advance Stage Parkinson's Disease

Completed Phase II Trials

One rotigotine subject (10%, 1/10) withdrew from trial SP533 for an adverse event (Study report). Subject 205/605 withdrew for QT prolonged (narrative summarized above in the SAE section). Four rotigotine subjects (11.8 %, 4/34) withdrew from study SP591 for adverse events (Study report). The AEs leading to discontinuation from study SP591 were hypertension (08/1005), hallucination

(10/1007), and application site reaction (10/1008, 13/1039). Nineteen rotigotine subjects (8.5%, 19/224) withdrew from study SP511 for adverse events. The AEs leading to discontinuation for rotigotine subjects were blood pressure increased (1706/42010); dizziness (0604/12020, 2501/12005); syncope, diplopia, nausea, chills, headache, vomiting (0905/22052); nausea and vomiting (1204/22012, 3408/32020); myocardial infarction (1508/22078); hallucination, disorientation (0303/12010); muscle stiffness/shaking, sensory hallucinations (4501/12078); application site reaction (0106/12054, 0405/12070,0101/12029); skin disorder blisters (0509/12047); laboratory test abnormal (CK 183, ULN 170; 1512/22079); bruise (2504/12006); skin disorder (6007/32094); dyskinesia (011/12063); nausea, dyskinesia, concentration impaired (3302/32085); headache, vomiting, angina pectoris, blood pressure high, palpitation (4802/42037).

Phase III Trials
In SP650 part I, 16% (36/229) of rotigotine subjects and 8% (10/120) of placebo subjects discontinued for AEs. In the following table I summarize the AEs leading to discontinuation of more than one rotigotine subject.

Adverse Event	Placebo (n=120)	Rotigotine (n=229)
Nausea	0	3% (8)
Vomiting	0	2% (5)
Hallucination	<1% (1)	2% (5)
Parkinson's disease	<1% (1)	2% (4)
Dyskinesia	0	2% (4)
Dizziness	0	1% (3)
Application site erythema	0	<1% (2)
Tremor	0	<1% (2)
Myocardial infarction*	0	<1% (2)

From Safety Update, Table 41.1, pp. 512-6.
* These two events were coded by the sponsor separately as myocardial infarction and myocardial infarction acute but are presented together by the reviewer.

The remaining AEs leading to discontinuation for rotigotine subjects in this study were application site dermatitis, application site pruritis, death, oedema peripheral, fall, electrocardiogram QT corrected interval prolonged, freezing phenomenon, cerebrovascular accident, headache, paranoia, sleep attacks, hyperhidrosis,

Through the data cutoff date, 5% (13/256) of subjects experienced a treatment emergent AE that led to discontinuation from study SP650 Part II. The AEs leading to discontinuation were cardiac failure, hallucination, somnolence, dizziness, confusion, Parkinsonism aggravated, nausea, gastrointestinal disorder NOS, cholecystitis, hepatitis cholestatic, oedema peripheral, muscle weakness, suicide attempt, and herpes zoster (Safety Update, Study report, Table 6, pp.158-9).

Restless Legs Syndrome
One subject discontinued from trial SP628 for an adverse event (80022, ventricular and supraventricular extrasystoles). No rotigotine subjects withdrew from study SP666 for adverse events. In study SP709, 4% (12/341) of rotigotine subjects discontinued for adverse events. The treatment emergent AEs leading to discontinuation from SP709 were nausea (n=5), application site reaction (n=2), rash erythematous (n=2), allergic reaction, fatigue, heart disorder, vomiting, QT

increased, and pruritis. In study SP710, through the data cutoff date, 7% (14/209) of subjects discontinued for AEs. The treatment emergent AEs that led to discontinuation were application site reaction (n=8), insomnia (n=2), hypotension, syncope, neuropathy, gastrointestinal disorder NOS, dermatitis contact, and rash.

Other Trials

From my review of the study reports from Phase I studies of silicone based rotigotine patches (n=660), I identified 10 rotigotine subjects who discontinued for treatment emergent adverse events. In the following table I identify the subjects and the adverse events that led to their discontinuations.

Study/Subject	AE leading to Discontinuation
SP502/11	Nausea, vomiting
SP502/15	Application site reaction, nausea, drowsiness, dizziness, trembling, chills, tremor, hallucination visual, sinking feeling, anxiety, speech disorder, numbness localized
SP626/7	Syncope, nausea, vomiting, dyspepsia
SP626/20	Syncope, nausea, vomiting
SP717/10023	Nausea, vomiting
SP717/10026	Nausea, vomiting
SP718/10023	Headache, nausea
SP718/10033	Vomiting
SP673/80070	Application site reaction
SP673/80238	QT increased

From individual study reports and Summary of Clinical Safety, p.105

There were 2 rotigotine subjects from Phase I study SP630 in 70 early stage Parkinson's disease patients who discontinued for treatment emergent adverse events (Study reports). Subject SP630/80316 discontinued for postural hypotension and subject SP630/80301 discontinued for anxiety.

In the three dose range finding iv trials (N-0923-001-2601, N-0923-002-01, and N-0923-006-01) in which 29 patients were exposed to rotigotine, I identified 9 subjects who discontinued for treatment emergent adverse events (Trial reports). From trial N-0923-001-2601, subjects #2 and #4 discontinued for premature atrial contractions. Subjects #7 and #8 discontinued for premature ventricular contractions. Subject #10 discontinued for both premature atrial and ventricular contractions. From study N-0923-006-01, subjects #9 and #11 discontinued for hypertension, subject #10 discontinued for hypotension, and subject #2 discontinued for ventricular tachycardia.

For the 86 rotigotine exposed subjects enrolled in 4 studies that used prototype patches (TD-0923-001, TD-0923-002, TD-0923-003, and TD-0923-004), I identified three subjects who discontinued for treatment emergent adverse events (Study reports). From trial TD 0923-002, subject #6 discontinued for ventricular tachycardia and subject #4 discontinued for a burning sensation in the chest. From study TD 0923-004, subject 0036 discontinued for postural hypotension.

Review of Discontinuation Due to Adverse Event Narratives

Ventricular Extrasystoles

SP628/ Subject 80022 This 64-year-old male subject with Restless Legs Syndrome discontinued from a pharmacokinetic trial for ventricular extrasystoles. The subject has a remote history of tobacco use (quit 30 years prior), and occasionally consumed alcohol and caffeinated beverages. He had no known heart disease. From 18 Mar 2003 onwards the patient was administered carbidopa 25mg/levodopa 100mg twice daily. On the evening of 19 Mar 2003 a single ventricular extrasystole was observed on the ECG monitor (at this time the patient was given carbidopa 25mg/levodopa 100mg only). From 20 Mar 2003 the patient was administered a combination therapy: carbidopa 25mg/levodopa 100mg twice daily and 4.5mg rotigotine transdermal patch. On the third day (22 Mar 2003) of the combination therapy, a cardiac arrhythmia (reported term: disordered action of the heart) was observed. In the evening of the fourth day (23 Mar 2003, 19:52 hours) of the combination therapy, "polytope" ventricular extrasystoles and supraventricular extrasystoles occurred (over 5 minutes enumerated), projecting to approximately 600/hour. The rotigotine patch was removed (20:06 hours) and therapy with carbidopa 25mg/levodopa 100mg was discontinued. Subjectively, the subject showed no symptoms. After removal of the patch, at 23:52 hours, no cardiac arrhythmia was observed on the ECG monitor. In the measurements recorded between 22 and 27 Mar 2003, QTc values ranged between 400 and 440ms (mean of 3 pre-dose measurements: 406ms). No clinically relevant findings were observed in laboratory examinations and vital signs during the trial. A cardiac examination was performed and no cardiac disease was found. After consulting the cardiologist and neurologist, the patient started treatment with Cabaseril® (cabergolin) 2mg daily since the evening of 26 Mar 2003. By recommendation of the cardiologist the patient was advised to repeat an ECG at his family doctor in 2 to 3 weeks. The AE was assessed to be possibly related to the trial medication.

> Summary of cardiologist's report, dated 12 May 2003:
> On the third day (22 Mar 2003) of combined treatment with carbidopa 25mg/levodopa 100mg and transdermal rotigotine, the subject developed supraventricular and ventricular cardiac arrhythmia. The trial medication was discontinued on the fourth treatment day. On the next day (24 Mar 2003), an exercise ECG up to 125 Watt was performed, and no pathological changes were found; only singular supraventricular extrasystoles were observed. In the echocardiography a minimal reflux at the mitral valve was observed. A long-term ECG (24 hours) showed 1300 monomorphic extrasystoles, and 5800 supraventricular extrasystoles were recorded. No tachycardia or repetitive extrasystole was detected. A long-term ECG was repeated by the primary care physician: The number of extrasystoles had decreased (approximately 200 ventricular extrasystoles, 1200 supraventricular extrasystoles) in comparison to the first long-term ECG.
> The subject did not report any subjective symptoms. He did not receive any concomitant medication. He had no history of a cardiovascular disease.
>
> Cardiologist's assessment:
> The subject was judged to be healthy regarding the results of the cardiac examinations. The finding at the mitral valve may be indicative for a carditis in the past. The increased cardiac arrhythmia during trial participation and in the first long-term ECG in comparison to the long term ECG done 2 weeks later was interpreted as an increased sympathetic activity, which was probably induced by the administered trial medication. Cardiac arrhythmias are known to appear in healthy subjects, and it is known that there is a high variation in the frequency. It cannot be excluded with certainty that factors other than the trial medication were contributory to the arrhythmias recorded during the trial participation. However, the overall risk for the patient can be assessed as low and no treatment or further actions are needed.

SP540/ Subject 000501 This 73 year old male with Parkinson's disease, hypertension, and ischemic heart disease, discontinued for ventricular extrasystoles. Fifteen days after entering the trial and while in the 9mg dose escalation phase of the study, the subject experienced multiple episodes of ventricular extrasystole recorded on a 12 lead ECG. He was advanced to a 13.5mg dose but was withdrawn from the study the next day for the extrasystoles. The narrative did not report any symptoms associated with this event. The narrative noted that the ECG at the post treatment follow up visit was reported as within normal limits. Medications taken prior to the study were amantadine and nifedipine.

QT increased

SP673/Subject 80238, This 48-year old, female subject was withdrawn from the trial due to the treatment emergent AE "QT increased." This event was moderate in severity, but did require the discontinuation of trial medication. This event resolved completely. This treatment emergent AE was not serious but was considered to be probably related to the trial medication. Re-analysis of 7 ECGs was done with computer assisted, manual point-to-point determination using image analysis software. Manual reading revealed pronounced flattening of T waves in the majority of leads. In some recordings, T waves in precordial leads were almost isoelectric or discretely negative. Manual measurement revealed normal QT and rate corrected QT values without significant increase after drug exposure. Thus, the marked difference in QTcB as calculated by the ECG machine was considered incorrect because of inadequate determination of the end of the T wave.

SP513/Subject 103606, This 50 year old female with Parkinson's disease discontinued from a trial after experiencing QTcB prolongation. The subject's pretreatment QTcB results were 450msec, 413msec, 440msec, and 424msec. Her on treatment QTcB results were 365msec, 408msec, 477msec, 494msec (withdrawal), and her follow up QTcB was 471msec. Her only other reported AEs during the trial were lower limb edema and periorbital edema.

SP513/Subject 104404, a 51 year old male with Parkinson's disease discontinued from a trial after experiencing QTcB prolongation (only reported AE). His pretreatment QTcB results were 365msec, 400msec, 400msec, and 415 msec. His on treatment QTcB results were 426msec, 418msec, 480msec, and 475msec. His date of last rotigotine administration was 4/2/03. His post treatment QTcB on 4/28/03 was reported as 700msec and the text description of that tracing reported ventricular tachycardia.

SP533/ Subject 205/605 Summarized above with SAEs

SP506/ Subject 1355 This 71 year old male with a history of sinus bradycardia, first degree AV block, left anterior hemiblock, essential hypertension, chest surgery, and Parkinson's disease discontinued from a trial for QTc prolonged. During the titration period, while receiving rotigotine 13.5mg/day, he experienced an increase in QTcB of >60msec from baseline. His baseline QTcB was 357msec (QTcF 365msec), which increased to a QTcB of 436msec (QTcF 427msec) and led to discontinuation. At his follow up visit following discontinuation, his QTcB was 413msec (QTcF 415msec).

SP512/ Subject 13004 This 64 year old male with a history of back pain, excessive sleepiness, glaucoma, coronary artery disease and stent placement, hypertension, hypothyroidism, and Parkinson's disease discontinued for QTc prolongation. During the dose titration period, while receiving rotigotine 4.5mg/day, he experienced an increase in QTc >60msec from baseline. On the same day he experienced ST wave changes. His QTc (cardiologist over read) values were 425msec (baseline), 484 msec (value leading to d/c), and 432 msec (follow up). The ST wave changes were also reported as resolved on the follow up ECG. Concomitant medications were acetylsalicylic acid, levoxyl, nitroglycerin, vitamin D, calcium, vitamin E, multivitamin, diltiazem, lananoprost eye drops, selegeline, brimonidine eye drops, and acetaminophen.

SP650 Part I/ Subject 13905 Narrative provided in 9/02/05 submission- This 83 year old male with a history of congestive heart failure, atrial fibrillation, cataracts, degenerative joint disease, Crohn's disease, Parkinson's disease, and other medical problems, discontinued for QTc prolongation. This subject's baseline QTcB was 428msec (investigator-read). Approximately four months later, he had a QTcB of 493msec (investigator-read) that led to discontinuation. Schwartz reported that a central over-read of the ECGs reported a baseline QTcB of 449msec and a QTcB leading to termination of 474msec. The central over-read did not confirm the QTcB prolongation. Follow up QTcB (investigator-read) was 403msec.Concomitant medications included digoxin, vitamin B12, carbidopa/levodopa, furosemide, K-dur, folic acid, acetaminophen, loperamide, tamsulosin, warfarin, fluticasone, diphenoxylate, flunisolide, sertraline, and pramipexole.

SP709/ Subject 10423 No narrative provided, information from CRF. This 63 year old male with a history of insomnia, reflux esophagitis, cardiac dysrhythmia, pacemaker placement, and restless leg syndrome discontinued from a trial for QTcB prolonged. The subjects first study ECG (screening) was notable for first degree AV block, with a machine measured QTcB of 442msec. The baseline QTcB (mean of three recordings) was 452msec. The subject discontinued

from the trial (last dose of study medication was 7 days after baseline ECG) for significant increase of QTcB but I could not locate an ECG recorded after the baseline ECGs. The CRF did not include the QTcB measurement that led to discontinuation.

Premature atrial contractions

N-0923-001-2601 Subjects #2 (61 year old male) **and #4** (39 year old male). Narratives were not provided in the study report for these subjects but their AEs were briefly discussed in the adverse event section. The sponsor included the following descriptions of these AEs in the study report:

Asymptomatic PACs were detected during Phase A on the bedside monitor in patients #002 and #004 immediately after the N-0923 10 minute infusions were completed. These resolved spontaneously within 40 to 60 minutes and required no medical intervention. The Investigator noted that the frequency of Patient #002's PACs was "a few" and that Patient #004 initially displayed "15-20 [PACs] per minute with gradual resolution over about 1 hour." The occurrence of PACs in these two patients in Phase A prompted the initiation of Holter monitor recording in all subsequent patients.

Both subjects had levodopa/carbidopa identified as concomitant medications. In Table 2, patient accountability, on page 32 of the study report, the sponsor reported that subject #2 received infusions of placebo, rotigotine 6mg/kg/hr, 9mg/kg/hr and 12mg/kg/hr and that subject #4 received infusions of placebo, and rotigotine 6mg/kg/hr.

Premature Ventricular Contractions

N-0923-001-2601 Subjects #7 (68 year old male) **and #8** (73 year old female). Narratives were not provided in the study report for these subjects but their AEs were briefly discussed in the adverse event section. The sponsor included the following descriptions of these AEs in the study report:

Patient #007: The investigator noted an "increased frequency of premature ventricular contractions" from 180 to 210 minutes into the infusion of 3mg/kg/hr N-0923 on 6/09/92. This observation was confirmed by the Holter monitor recording, which detected 1, 9, 125, and 222 isolated PVCs before and during the first, second and third 60 minute periods of the infusion, respectively. Patient #007 complained of nausea, lightheadedness, drowsiness, yawning, and headache, and the investigator found orthostatic hypotension at the same time, with supine and standing blood pressures 133/77 and 88/58, respectively. During the 19 hours following the infusion, Patient #007 experienced 41 to 184 asymptomatic PVCs per hour, none of which were noted as AEs. Abnormal ECG findings ("ventricular premature complex, short R-R interval and wide QRS") were noted when Patient #007 was enrolled into the study. The patient experienced frequent PACs (996/24 hours) on the placebo infusion day and frequent PVCs on each other treatment day, but none of these were recorded as AEs by the Investigator. It is possible that the occurrence of nausea and orthostatic hypotension, which are predictable side effects of dopamine agonists, misinterpretation of description of PVC morphology may have contributed to the ectopic activity that was described as an AE.

Patient #008: The investigator reported 30 minutes of PACs starting 210 minutes into the infusion of 2.5µg/kg/hr N-0923 on 6/12/02. The Holter monitor detected 11 to 22 PVCs during this time, and the patient also reported concurrent drowsiness and sweating. The Investigator reported 20 minutes of PVCs beginning 90 minutes into the infusion of 3.5µg/kg/hr N-0923 on 6/15/92. The Holter monitor detected 42 isolated PVCs during this time, with the patient noting concurrent drowsiness and weakness. Six hours later on the same day, the Holter monitor recorded 59 PVCs, but these were not recorded as AEs.

Both subjects had levodopa/carbidopa identified as concomitant medications.

The table below summarizes Holter monitor data for subject #007.

Summary of Holter Monitor Data: N-0923/001, Phase B: Patient #007					
Placebo, or Dose N-0923 (µg/kg/hr)	Date of Treatment (m/d/yr)	Duration Monitored	Number Supraventricular Ectopic Beats	Number Ventricular Ectopic Beats	Hear Rate: Min-Max; Avg
Placebo	06/02/92	23 hr, 14 min	996: 994 isolated,	149 isolated	57-123; 90

			1 couplet		
0.50	06/03/92	23 hr, 56 min	7 isolated	775 isolated	56-118; 89
1.00	06/04/92	8 hr, 26min	7: 4 isolated, 1 run (3 beats)	886 isolated	63-120; 91
1.50	06/05/92	6 hr, 38 min	35: 14 isolated, 2 couplets, 1 run (17 beats)	575 isolated	69-114; 90
2.00	06/08/92	7hr, 57min	2 isolated	569 isolated	65-123; 93
3.00	06/09/92	23hr, 24min	115: 90 isolated, 3 couplets, 3 runs (9 beats)	2386 isolated	56-130; 89

Study report, p.449
Holter data extrapolated to 24 hours to allow for comparisons

Holter monitor data were reviewed by — For subject #007, — felt that the data did not support an association between N-0923 and extrasystoles. — noted that the subject had 996 PACs on the placebo day compared to 7 PACs when 0.5 µg/kg/hr was infused. They also noted that the subject experienced more PVCs on treatment days but that there was no dose relationship.

The table below summarizes Holter data for subject #008

Summary of Holter Monitor Data: N-0923/001, Phase B: Patient #008					
Placebo, or Dose N-0923 (µg/kg/hr)	Date of Treatment (m/d/yr)	Duration Monitored	Number Supraventricular Ectopic Beats	Number Ventricular Ectopic Beats	Hear Rate: Min-Max; Avg
Placebo	06/04/92	23 hr, 46 min	58: 42 isolated, 1 couplet, 1 run (14 beats)	9 isolated	44-121; 84
0.50	06/05/92	6 hr, 8 min	8: 3 isolated, 1 couplet, 1 run (3 beats)	11 isolated	74-125; 97
1.00	06/08/92	7 hr, 18min	3 isolated	10 isolated	65-120; 91
1.50	06/09/92	6 hr, 59 min	6 isolated,	3 isolated	69-123; 90
2.00	06/11/92	7hr, 43min	3 isolated	21 isolated	69-121; 92
2.50	06/12/92	7hr, 15min	19 isolated	59: 57 isolated, 1 couplet	67-134; 95
3.50	6/15/92	24hr, 15 min	25: 23 isolated, 1 couplet	248: 244 isolated, 3 bigeminal cycles, 2 couplets	44-120; 82

Study report, p.450
Holter data extrapolated to 24 hours to allow for comparisons

— elt that the Holter data supported that "doses less than 3.5 µg/kg/hr were not associated with extrasystoles and that a possible association of the highest dose is equivocal." — acknowledged a higher incidence of PVCs on treatment days compared to placebo but felt there was no clear relation to dose.

Premature atrial and ventricular contractions

N-0923-001-2601 Subject #10 (57 year old male) A narrative was not provided in the study report for this subject but the AE was briefly discussed in the adverse event section. The sponsor reported the following: Patient #010: On the AE form, the Investigator reported 240 minutes of PACs starting 60 minutes into the placebo infusion on 08/04/92; he recorded this as "few PACs" from 60 to 240 minutes on the ETB (MCRS) Rating Sheet (for motor performance) for that day. The Holter monitor did not detect any PACs during this time. The investigator reported 120 minutes of PACs

starting 60 minutes into the 6µg/kg/hr infusion of N-0923 on 8/13/92. The Holter monitor recorded only 2-4 isolated PACs per 60 minutes during this time. The Investigator also reported 120 minutes of premature atrial and ventricular contractions starting 30 minutes into the infusion of 5µg/kg/hr N-0923 on 8/12/02. The Holter monitor detected two or fewer PVCs per hour and three or fewer PACs per hour during this time. No AEs were recorded on other treatment days, in spite of a similar occurrence of PACs and PVCs on most study days.

The table below summarizes Holter data for subject #010

Summary of Holter Monitor Data: N-0923/001, Phase B: Patient #010					
Placebo, or Dose N-0923 (µg/kg/hr)	Date of Treatment (m/d/yr)	Duration Monitored	Number Supraventricular Ectopic Beats	Number Ventricular Ectopic Beats	Hear Rate: Min-Max; Avg
Placebo	08/04/92	21 hr, 32 min	1 isolated	3 isolated	45-187; 69
0.50	08/05/92	7 hr, 2 min	None	4 isolated	52-156; 85
1.00	08/06/92	9 hr, 27min	33: 31 isolated, 1 run (3 beats)	17 isolated	49-114; 72
2.00	08/07/92	6 hr, 41 min	14 isolated,	10 isolated	58-166; 90
3.00	08/10/92	8hr, 28min	27: 23 isolated, 2 couplets	2 isolated	51-108; 66
4.00	08/11/92	6hr, 41min	None	6 isolated	49-156; 88
5.00	8/12/92	8hr, 37 min	26 isolated	9 isolated	52-116; 70
6.00	8/13/92	18hr, 47 min	53 isolated	6 isolated	52-153; 75
6.00	8/14/92	No data	No data	No data	No data

Study report, p.452
Holter data extrapolated to 24 hours to allow for comparisons

felt the available data did not support an association between the study drug and extrasystoles. When they focused on the events during infusion, commented that the frequency of ectopic beats was not greater during infusion of the study treatment or placebo than at other times during the monitoring periods.

Ventricular Tachycardia

TD 0923-002 Subject #6 (68 year old female) A narrative was not provided in the study report for this subject but the AE was briefly discussed in the adverse event section. The sponsor reported the following: Eighteen minutes following removal of the N-0923 TDS patches from Patient 06, a six beat run of ventricular tachycardia (VT) was recorded by Holter monitor (but not by ECG telemetry). This was not sustained but terminated spontaneously; it was monomorphic and was not associated with any clinical symptoms. The concentration of N-0923 in the plasma at the closest sampling time (immediately before removing the patch 18 min earlier) was 0 nL. The plasma concentration 6 hrs earlier (when the patch had been applied for 24 hrs) was ng/mL, and 42 min after the run of VT wa: ıg/mL. No other ectopic events occurred during this period of stable plasma concentrations. Thus the occurrence of the VT was not associated with an increase in the plasma concentrations of N-0923. It is unknown whether this event was related to N-0923 because frequent ectopy and non-sustained runs of VT are common in elderly patients. However, as a safety precaution, the Investigator decided to discontinue this patient from the study.

The table below summarizes Holter data for subject #06

Summary of Holter Monitor Data: TD 0923/002, Patient #06			
Placebo, or Dose N-0923 (µg/kg/hr)	Duration Monitored (hours)	Number Supraventricular Ectopic Beats*	Number Ventricular Ectopic Beats*
Screening	24.95	21	10
Baseline 1	18.38	37	12
Treatment 1	24.77	28	17

Study report, p.652-4.

*Normalized to 24 hours
N-0923-006-01/ Subject #2/JJH Summarized above with SAEs

ECG abnormal

Three subjects (SP506 001556, SP512 011204, and SP512 013004) were identified as discontinuing for AEs of ECG abnormal. SP506 subject 001556 experienced T3 sagging in the inferolateral lead and SP512 subject 011204 experienced non-specific T-wave changes. SP512 subject 013004 experienced ST changes and prolonged QT interval and that event is summarized with the other QT prolongation events.

SGOT increased

SP534/ Subject 000109 This 62 year old male with a past history of hepatitis (etiology not specified) and Parkinson's disease discontinued for headache, nausea, and SGOT increased. The subject's baseline transaminase results were elevated (SGPT 79IU/L, SGOT 86IU/L) and total bilirubin was normal (0.8mg/dL). At the time of discontinuation, his SGPT was 69IU/L, SGOT was 132IU/L, and total bilirubin was 1mg/dL. The event was not considered related to trial medication due to the elevated baseline lab values, the history of hepatitis and the subject's reported history of ingesting 72 ounces of alcohol per day.

Leukopenia

SP535/ Subject 000312 This 38 year old male with Parkinson's disease experienced mild thrombocytopenia and leucopenia that were identified following a placebo run in period, prior to first rotigotine dose. The subject's baseline WBC count was 5.6 and platelet count was 165. After completing the placebo run in, his WBC was 4.4 and platelet count was 161. His results on rotigotine were WBC 4.3, platelets 135 and WBC 3.8, platelets 111. Subsequent to drug discontinuation, his follow up WBC count was 6.1 and platelet count was 175. Concomitant medications at the time of the AEs were ascorbic acid, tocopherol, coenzyme Q10, citalopram, and amantadine.

Rash Maculopapular

SP512 Part 1/ Subject 12704 This 52 year old female with a history of hypercholesterolemia, anemia, stress incontinence, hypothyroidism, and Parkinson's disease discontinued for maculopapular rash. The rash started after 75 days of study drug treatment and she was taking rotigotine 13.5mg/day at the time of the event. The rash was described as a diffuse, generalized itchy maculopapular rash. In addition to the generalized rash, the subject also experienced an application site reaction. Concomitant medications included conjugated estrogen, progesterone, levothyroxine, and calcium.

Bullous eruption, Rash Maculopapular

SP506/ Subject 03308/1457, a 52 year old female with a history of bilateral ear surgery, mild hearing loss, and Parkinson's disease developed an application site reaction 41 days after starting trial medication. Her rotigotine dose at the time of the event was 18mg/day. The reaction was described as a severe bullous eruption that evolved from previous application site reactions and spread to involve the entire abdominal area, groin, left wrist, and neck. The reaction also included raised papular erythematous lesions on the anterior and posterior neck, left forearm, and bilateral inguinal areas. Trial medication was stopped and the event was ongoing at follow up. The narrative included no information about treatment. Concomitant medications at the time of the event were calcium, vitamin D, multivitamin, diphenhydramine cream as needed, hydrocortisone cream as needed.

Rash Erythematous

SP513 Part 1/ Subject 100501 This 36 year old female with a history of appendectomy, and Parkinson's disease discontinued for a rash. The subject developed what was described as a generalized urticarial exanthema that started on the second day of rotigotine treatment (4.5mg/day). She was treated with dimetindene and topical methylprednisolone. The subject recovered from this event. Concomitant medication included desogestrel and ethinylestradiol.

SP709/ Subject 12312 No narrative provided, information from CRF. This 27 year old female discontinued from a study for rash erythematous, and application site reaction. The rash was not described in the CRF. The event was reported as resolved.

SP709/ Subject 10207 No narrative provided, information from CRF. This 66 year old female discontinued from a study for rash erythematous. The rash was not described in the CRF. The event was reported as resolved.

SP513DB/Subject 101203/801203 Summarized above with SAEs.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Schwarz explained in the Safety Update that investigators were instructed to report any AE experienced by subjects during trial participation (SU, p.43). Schwarz did not describe the use of checklists to capture AEs and checklists were not present in the submitted CRFs. Study subjects were assessed for AEs at each trial visit. Analysis pool S3 included data from the following early-stage PD Phase II/III trials: 506 (12 weeks duration), 512 (27 weeks controlled followed by 12 months OL duration), 513 (up to 37 weeks controlled followed by 12 months OL duration), 534 (8 weeks total duration for parts I and II), 535 (4 weeks duration) and 540 (28 days duration). For study 506, subjects were assessed for AEs on study days -28 to -4 (screening), 0 (baseline), 8 or 9, 14, 22 or 23, 28, 49, 77, 84-86, and 98 (Study 506 Study Report). For study 512, subjects were assessed for AEs on study days -28 to -1 (screening), 0 (baseline), 8, 15, 29, 57, 85, 113, 141, 169, and 197 (Study 512 Study Report). For study 513, subjects were assessed for AEs on study weeks 1, 2, 3, 4, 5, 13, 25, 37, and 49 (Study 513 Study Report). In the open label extensions of trials 512 and 513, subjects were assessed for AEs every 12 weeks. For study 534 parts I and II, subjects were assessed for AEs on days -7 (screening), 1, 2, 3, 4, 5, 8, 15, 22, 29, and 57. For trial 535, subjects were assessed for AEs on days -7 (screening), 1, 4, 8, 11, 15, 18, 22, 25, 29, 36, and 57. For trial 540, subjects were assessed for AEs on days -7 (screening), -1, 1, 2, 8, 9, 15, 16, 22, 23, and 29.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Schwarz's approach to the coding and classification of adverse events was acceptable. Schwarz noted that "The coding of AEs in trials SP512 and SP513 was currently performed and was considered to be fixed, whereas for the older trials coding were re-checked to ensure consistent coding for the data pools." Schwarz classified AEs that occurred or worsened on or after the start of trial drug including 1 day after patch removal as treatment emergent. Schwarz classified AEs that occurred during the 30 day follow up period as treatment emergent during 30 day safety follow up (SU p.44). For dose response analyses, AEs were assigned to the dose administered at the time of the AE. For AEs that occurred on days of patch changes, the event was assigned to the lowest rotigotine dose. If an AE occurred during a medication gap during transition from a double blind period to an open label period, the AE was assigned to the double blind period treatment group and the dose was denoted as no dose (SU, p.44).

Schwarz coded verbatim AE terms from early-stage PD trials using the SCHWARZ PHARMA modified version of the 1993 WHO-ART dictionary (SU, p.43). I assessed Schwarz's coding of adverse event verbatim terms to preferred terms. For adverse events that had narratives (deaths,

serious AEs, AEs leading to withdrawal), I compared the events described in the narratives to the preferred terms assigned to these events. I also reviewed SU table 68.2 to compare the verbatim terms to the assigned preferred terms for pool S3 studies. In addition, I reviewed the body system groupings of AE preferred terms.

In general, the coding of verbatim terms to preferred terms was appropriate and should have allowed for an accurate assessment of the AEs observed during the development program. There were occasional exceptions where Schwarz grouped potentially unrelated events under a single preferred term, split related events to different preferred terms, and assigned verbatim terms to an inappropriate preferred term. An example of grouping unrelated terms was the use of the preferred term cyst. This grouping included unrelated events such as Baker's cyst, sebaceous cyst, and ganglion cyst. Another example of grouping unrelated events under a preferred term was the use of the preferred term surgical intervention. This preferred term included the unrelated events of basal cell cancer removal, cataract surgery, and cholecystectomy. An example of splitting of related terms was the use of several preferred terms for edema related events. For example Schwarz used the preferred terms oedema dependent and oedema peripheral and both preferred terms included verbatim terms of ankle edema and foot edema. It was not clear why ankle edema would be coded to oedema dependent in one case and oedema peripheral in another. Furthermore, oedema events were split to an even greater extent by including them in more than one body system. The grouping of Body as a Whole included the preferred terms face oedema, oedema dependent, oedema legs, and oedema peripheral. The grouping of Cardiovascular Disorders, General included the preferred terms oedema dependent, oedema legs, oedema peripheral, oedema, oedema generalized, and oedema periorbital. The grouping of Gastro-intestinal System Disorders included the preferred term oedema mouth. The grouping of Metabolic and Nutritional Disorders included the preferred terms oedema, oedema generalized, and oedema periorbital. Schwarz addressed problems related to coding of edema events in a separate analysis that is presented below. An example of inappropriate coding was the use of the preferred term myopathy. Schwarz coded the events contraction of the 4th digit L hand, plantar facsiitis, and tennis elbow to the preferred term myopathy.

7.1.5.3 Incidence of common adverse events
In the following section, I review Schwarz's presentation of adverse event data. In their presentations, Schwarz focused on AEs observed during the early-stage PD trials, the indication being sought by the sponsor. I present additional information from the study report for the advanced PD controlled trial SP650 Part I.

7.1.5.4 Common adverse event tables
Early Stage Parkinson's Disease Indication Phase II/III Trials, Pool S3
Schwarz provided a table that summarized common AEs (>=5%) from the controlled and open label phase II/III early-stage PD trials. I reproduce that table below.

Summary of Treatment Emergent AEs Occurring in >=5% of Rotigotine Treated Subjects- Pool S3

Body System/Preferred Term	Rotigotine (N=1093) % (n)
Any body system	87% (945)

Application site disorders	
Application site reactions	37% (401)
Central and peripheral nervous system disorders	
Dizziness	18% (191)
Headache	13% (146)
Gastro-intestinal system disorders	
Nausea	32% (350)
Vomiting	11% (121)
Constipation	6% (61)
Musculoskeletal system disorders	
Back pain	7% (75)
Psychiatric disorders	
Somnolence	23% (256)
Insomnia	11% (119)
Respiratory system disorders	
Upper respiratory tract infection	8% (83)
Secondary term	
Fall	7% (71)

From SU, p.47.

Early Stage Parkinson's Disease Phase II/III Controlled Trials, Pool S1
Using ISS table 23.1 from the NDA, I identified the AEs occurring in at least 1% of rotigotine subjects from early-stage PD controlled trials. I present that information below. The shaded events are those that occurred at least twice as frequently among rotigotine subjects compared to placebo subjects.

Pool S1 Studies Treatment Emergent AE Risks, for AEs Occurring in at Least 1% of Rotigotine Subjects.

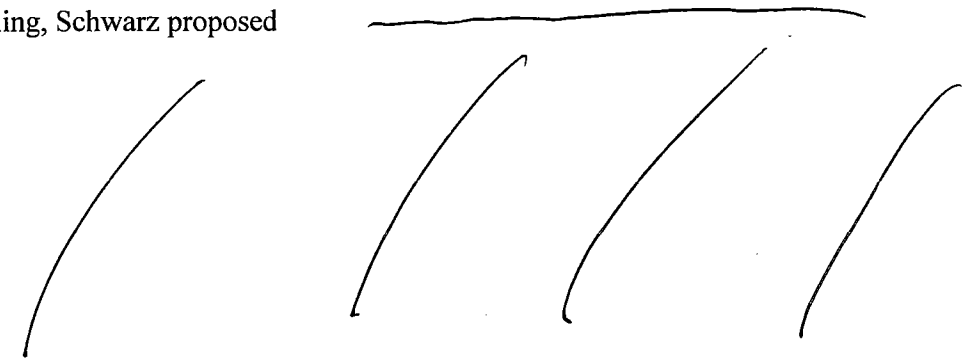
Body System/Preferred Term	Placebo N=289 % (n)	Rotigotine N=649 % (n)	Ropinirole N=228 % (n)
Any body system	**81.7% (236)**	**86.0% (558)**	**83.8% (191)**
Application site disorders	**13.8% (40)**	**36.8% (239)**	**7.5% (17)**
Application site reactions	13.8% (40)	36.8% (239)	7.5% (17)
Autonomic nervous system disorders	**7.6% (22)**	**9.6% (62)**	**7.9% (18)**
Sweating increased	2.4% (7)	3.5% (23)	3.1% (7)
Mouth dry	1.4% (4)	3.1% (20)	2.6% (6)
Hypotension postural	2.8% (8)	1.5% (10)	1.3% (3)
Body as a whole-General	**23.2% (67)**	**23.0% (149)**	**19.7% (45)**
Fatigue	6.9% (20)	7.6% (49)	6.1% (14)
Accident NOS	3.5% (10)	4.6% (30)	1.8% (4)
Asthenia	2.1% (6)	2.2% (14)	0.9% (2)
Influenza like symptoms	1.7% (5)	2.2% (14)	4.4% (10)
Chest pain	2.1% (6)	2.0% (13)	3.9% (9)
Pain	3.8% (11)	1.8% (12)	0.9% (2)
Leg pain	4.2% (12)	1.5% (10)	1.8% (4)

Malaise	1.4% (4)	1.4% (9)	1.8% (4)
Oedema peripheral	1% (3)	1.4% (9)	0
Fever	0.3% (1)	1.4% (9)	0.4% (1)
Cardiovascular disorders-General	**9.7% (28)**	**10.5% (68)**	**11.8% (27)**
Hypertension	2.1% (6)	3.1% (20)	4.8% (11)
Oedema peripheral	1.7% (5)	2.2% (14)	0.9% (2)
Oedema dependent	2.4% (7)	1.5% (10)	2.6% (6)
Syncope	0.7% (2)	1.1% (7)	3.1% (7)
Centr&periph nerv syst disorders	**33.6% (97)**	**38.1% (247)**	**35.1% (80)**
Dizziness	11.1% (32)	18.2% (118)	17.1% (39)
Headache	10.4% (30)	13.6% (88)	8.8% (20)
Tremor	4.2% (12)	3.4% (22)	0.9% (2)
Vertigo	1.7% (5)	2.5% (16)	3.5% (8)
Muscle contractions invol	1.0% (3)	1.8% (12)	0.9% (2)
Gait abnormal	0	1.8% (12)	0.9% (2)
Parasthesias	2.4% (7)	1.5% (11)	1.8% (4)
Cramps legs	1.0% (3)	1.5% (10)	0.9% (2)
Confusion	0.3% (1)	1.4% (9)	3.9% (9)
Neuralgia	1.7% (5)	1.1% (7)	0.9% (2)
Gastro-intestinal system disorders	**28.4% (82)**	**49.3% (320)**	**51.3% (117)**
Nausea	14.9% (43)	37.6% (244)	36.0% (82)
Vomiting	2.1% (6)	12.5% (81)	11.0% (25)
Constipation	3.8% (11)	5.4% (35)	8.8% (20)
Diarrhea	3.8% (11)	4.2% (27)	6.1% (14)
Dyspepsia	1.4% (4)	3.7% (24)	5.7% (13)
Anorexia	1.0% (3)	2.8% (18)	1.8% (4)
Abdominal pain	2.8% (8)	2.5% (16)	6.6% (15)
Hiccup	0	1.7% (11)	0.9% (2)
Gastroesophageal reflux	0	1.2% (8)	0.4% (1)
Heart rate and rhythm disorders	**6.2% (18)**	**6.0% (39)**	**4.8% (11)**
QT increased	0.3% (1)	1.2% (8)	0
Palpitation	0.7% (2)	1.1% (7)	0.9% (2)
Bundle branch block	0.7% (2)	1.1% (7)	0
Liver and biliary system disorders	**3.1% (9)**	**2.3% (15)**	**2.6% (6)**
Gamma-GT increased	0.7% (2)	1.1% (7)	0.4% (1)
Metabolic and nutritional disorders	**6.2% (18)**	**6.5% (42)**	**5.3% (12)**
Weight decrease	1.0% (3)	1.8% (12)	0.9% (2)
Hyperglycemia	0.7% (2)	1.4% (9)	1.3% (3)
Musculo-skeletal system disorders	**15.6% (45)**	**13.7% (89)**	**12.3% (28)**
Back pain	5.2% (15)	5.5% (36)	5.3% (12)
Arthralgia	3.1% (9)	3.7% (24)	3.1% (7)
Skeletal pain	3.5% (10)	2.3% 915)	0.4% (1)
Myalgia	1.7% (5)	1.8% (12)	1.3% (3)
Psychiatric disorders	**26.6% (77)**	**37.6% (244)**	**38.6% (88)**
Somnolence	15.6% (45)	24.8% (161)	29.4% (67)
Insomnia	4.8% (14)	9.9% (64)	6.1% (14)
Dreaming abnormal	0.3% (1)	3.4% (22)	0.4% (1)
Anxiety	3.5% (10)	2.9% (19)	2.2% (5)
Depression	1.7% (5)	2.3% (15)	0.9% (2)
Hallucination	0.7% (2)	2.0% (13)	5.7% (13)
Sleep attacks	0	1.4% (9)	1.8% (4)
Agitation	1.0% (3)	1.2% (8)	0.9% (2)

Resistance mechanism disorders	**3.8% (11)**	**3.4% (22)**	**4.8% (11)**
Infection	1.0% (3)	1.5% (10)	0.9% (2)
Respiratory system disorders	**15.2% (44)**	**17.6% (114)**	**15.8% (36)**
Upper Resp Tract Infection	5.5% (16)	5.2% (34)	5.3% (12)
Coughing	3.8% (11)	3.4% (22)	5.3% (12)
Sinusitis	2.4% (7)	2.8% (18)	1.8% (4)
Rhinitis	1.7% (5)	2.2% (14)	0.9% (2)
Pharyngitis	0	1.7% (11)	3.1% (7)
Bronchitis	1.7% (5)	1.5% (10)	1.3% (3)
Dyspnea	0.7% (2)	1.2% (8)	2.6% (6)
Secondary Terms	**10% (29)**	**5.4% (35)**	**8.3% (19)**
Fall	7.6% (22)	4.3% (28)	6.1% (14)
Skin and appendage disorders	**13.8% (40)**	**11.6% (75)**	**4.8% (11)**
Rash	3.1% (9)	2.5% (16)	1.3% (3)
Rash erythematous	0.7% (2)	2.3% (15)	0.9% (2)
Pruritis	1.4% (4)	1.8% (13)	1.3% (3)
Urinary system disorders	**7.3% (21)**	**8.5% (55)**	**4.4% (10)**
Urinary tract infection	1.4% (4)	2.8% (18)	1.8% (4)
Micturition frequency	1.7% (5)	2.0% (13)	0.9% (2)
Urinary incontinence	0.7% (2)	1.4% (9)	0.4% (1)
Pyuria	0.3% (1)	1.1% (7)	0
Vascular (extracardiac) disorders	**4.2% (12)**	**2.8% (18)**	**3.9% (9)**
Purpura	2.1% (6)	1.5% (10)	0.4% (1)
Vision Disorders	**2.8% (8)**	**4.3% (28)**	**2.6% (6)**
Vision abnormal	0.7% (2)	2.9% (19)	0.9% (2)

From ISS table 23.1

For labeling, Schwarz proposed



Advanced Stage Parkinson's Disease Phase II/III Controlled Trial, SP650
Using SU table 36.2.1, I identified the AEs occurring in at least 1% of rotigotine subjects from the advanced stage Parkinson's disease controlled trial SP650 (up to 38 weeks duration, up to 27mg). I present that information below. The shaded events are those that occurred at least twice as frequently when compared to placebo. The reason for differences in preferred terms in the following table compared to previous tables is that the AEs in study SP650 were coded using a different dictionary (MedDRA, version 7) than the AE dictionary used to code the AEs from the early-stage PD trials (WHO-ART) (SU p.119).

Study SP650 Part I Treatment Emergent AE Risks, for AEs Occurring in at Least 1% of Rotigotine Subjects.

Body System/Preferred Term	Placebo N=120 % (n)	Rotigotine N=229 % (n)
Any body system	**92% (110)**	**93% (214)**
Blood and lymphatic system disorders	**2% (2)**	**3% (6)**
Anemia	<1% (1)	1% (3)
Cardiac Disorders	**4% (5)**	**6% (14)**
AV block first degree	0	1% (3)
Palpitations	<1% (1)	1% (3)
Cardiac failure congestive	<1% (1)	1% (3)
Eye disorders	**6% (7)**	**7% (17)**
Visual disturbance	0	2% (5)
Cataract	<1% (1)	2% (4)
Gastrointestinal disorders	**38% (46)**	**40% (91)**
Nausea	18% (22)	25% (57)
Vomiting	6% (7)	9% (21)
Constipation	6% (7)	7% (16)
Diarrhea	4% (5)	6% (13)
Dry Mouth	6% (7)	3% (8)
Dyspepsia	2% (2)	2% (4)
Abdominal pain upper	3% (3)	1% (3)
Abdominal pain	0	1% (3)
General disorders and application site conditions	**32% (38)**	**55% (126)**
Application site erythema	3% (4)	20% (45)
Application site pruritis	3% (4)	16% (36)
Oedema peripheral	<1% (1)	11% (26)
Application site dermatitis	<1% (1)	7% (15)
Application site reaction	3% (3)	3% (8)
Fatigue	7% (8)	3% (7)
Asthenia	4% (5)	3% (7)
Application site irritation	2% (2)	3% (6)
Application site burning	2% (2)	2% (5)
Chest pain	3% (3)	2% (4)
Application site vesicles	0	2% (4)
Pain	3% (3)	1% (3)
Infections and infestations	**26% (31)**	**23% (52)**
Nasopharyngitis	5% (6)	7% (15)
Upper respiratory tract infection	5% (6)	4% (9)
Influenza	0	2% (4)
Bronchitis	0	1% (3)
Urinary tract infection	3% (3)	1% (3)
Localized infection	0	1% (3)
Cellulitis	<1% (1)	1% (3)
Herpes simplex	0	1% (3)
Injury, poisoning and procedural complications	**28% (33)**	**25% (58)**
Fall	18% (21)	14% (31)
Skin laceration	3% (4)	3% (6)
Excoriation	3% (3)	2% (4)
Contusion	7% (8)	1% (3)
Back injury	0	1% (3)

Rib fracture	<1% (1)	1% (3)
Investigations	**13% (16)**	**9% (20)**
Weight decreased	<1% (1)	2% (5)
Weight increased	0	1% (3)
Metabolism and nutrition disorders	**8% (9)**	**6% (13)**
Decreased appetite	<1% (1)	1% (3)
Musculoskeletal and connective tissue disorders	**36% (43)**	**24% (56)**
Arthralgia	7% (8)	10% (23)
Pain in extremity	7% (8)	5% (11)
Back pain	4% (5)	4% (9)
Muscle cramp	2% (2)	3% (6)
Muscle spasms	<1% (1)	1% (3)
Neoplasms benign, malignant, and unspecified	**5% (6)**	**3% (7)**
Basal cell carcinoma	<1% (1)	1% (3)
Nervous system disorders	**57% (68)**	**63% (144)**
Somnolence	28% (33)	32% (74)
Dizziness	15% (18)	19% (44)
Dyskinesia	7% (8)	15% (35)
Headache	8% (10)	9% (21)
Parkinson's disease	6% (7)	4% (9)
Parasthesia	2% (2)	3% (8)
Tremor	3% (4)	3% (7)
Freezing phenomenon	4% (5)	3% (6)
Hypoaesthesia	<1% (1)	2% (5)
Balance disorder	2% (2)	1% (3)
Dystonia	2% (2)	1% (3)
Lethargy	<1% (1)	1% (3)
Dizziness postural	<1% (1)	1% (3)
Psychiatric disorders	**18% (21)**	**30% (68)**
Insomnia	6% (7)	10% (23)
Hallucination	3% (3)	7% (15)
Depression	3% (4)	3% (7)
Nightmare	<1% (1)	3% (7)
Hallucination, visual	0	2% (5)
Confusional state	2% (2)	2% (5)
Abnormal dreams	0	1% (3)
Agitation	<1% (1)	1% (3)
Disorientation	0	1% (3)
Sleep disorder	0	1% (3)
Renal and urinary disorders	**7% (8)**	**6% (13)**
Pollakiuria	3% (3)	2% (4)
Urinary incontinence	2% (2)	1% (3)
Respiratory, thoracic and mediastinal disorders	**8% (10)**	**14% (33)**
Dyspnea	3% (3)	3% (6)
Cough	<1% (1)	3% (6)
Nasal congestion	0	3% (6)
Sinus congestion	0	3% (6)
Hiccups	0	1% (3)
Pharyngolaryngeal pain	<1% (1)	1% (3)
Skin and subcutaneous tissue disorders	**8% (10)**	**14% (33)**
Rash	3% (3)	3% (8)
Hyperhidrosis	0	2% (5)
Erythema	<1% (1)	2% (5)

Pruritis	2% (2)	1% (3)
Vascular disorders	**8% (10)**	**8% (19)**
Hypertension	0	4% (9)
Orthostatic hypotension	7% (8)	2% (4)
Flushing	<1% (1)	1% (3)

From Table 36.2.1, SP 650 Part I Tables for 120 day SU.

7.1.5.5 Identifying common and drug-related adverse events

To further evaluate the evidence supporting whether any of the AEs identified from the early-stage PD controlled trials could be drug related; I looked for consistently elevated risk by treatment across trials. For AEs occurring in at least 1% of rotigotine subjects and that were more common when compared to placebo in the above table, I examined the risks in the similarly designed early-stage PD studies 512 and 513. In the table below, I identify those events where the risk was elevated among rotigotine subjects compared to placebo subjects in both studies.

Comparison of Adverse Event Risk for Selected Adverse Events from Trials SP512, and SP513

Preferred Term	Study 512		Study 513	
	Placebo (n=95)	Rotigotine (n=181)	Placebo (n=118)	Rotigotine (n=215)
Application site reactions	12% (11)	44% (79)	11% (13)	38% (81)
Fever	0	1% (2)	0	1% (3)
Hypertension	1% (1)	4% (8)	3% (4)	5% (10)
Dizziness	13% (12)	19% (34)	10% (12)	14% (30)
Headache	9% (9)	16% (29)	8% (10)	10% (21)
Vertigo	2% (2)	3% (5)	3% (3)	4% (9)
Gait abnormal	0	3% (5)	0	2% (5)
Cramps legs	2% (2)	3% (5)	0	2% (4)
Confusion	1% (1)	3% (5)	0	<1% (1)
Nausea	17% (16)	41% (75)	16% (19)	29% (63)
Vomiting	1% (1)	9% (16)	3% (4)	12% (26)
Constipation	4% (4)	6% (11)	4% (5)	7% (14)
Dyspepsia	1% (1)	7% (12)	2% (2)	3% (7)
Hiccup	0	2% (4)	0	<1% (2)
Somnolence	20% (19)	33% (60)	20% (24)	23% (50)
Insomnia	3% (3)	9% (17)	5% (6)	6% (13)
Dreaming abnormal	0	4% (8)	<1% (1)	1% (3)
Sleep attacks	0	1% (2)	0	3% (6)
Infection	2% (2)	3% (6)	<1% (1)	1% (3)
Pharyngitis	0	1% (2)	0	3% (6)
Rash erythematous	0	1% (2)	<1% (1)	2% (4)
Urinary tract infection	1% (1)	2% (3)	<1% (1)	5% (11)
Urinary incontinence	2% (2)	3% (5)	0	<1% (1)

AE data from Study reports 512 table 24.2.1, and 513 Table 24.2.1

7.1.5.6 Additional analyses and explorations

Schwarz presented dose response analyses for AEs but interpretation of these analyses is difficult. In most cases, subjects were randomized to target doses or were titrated to an optimal dose. Studies also generally allowed back titration. In studies that allowed dose switching, subjects were not randomized to the dose received but instead took the dose they tolerated. Although this approximates what would occur in a real world setting, it impacts interpretation of the dose response data. Schwarz

took a consistent approach in classifying dose at which the AE occurred but a potential concern is the method Schwarz used to calculate dose group denominators. Table 24.1 classified study subjects by the rotigotine dose that they took for the longest duration and then provided AEs risks for these groupings. It is possible that patients who experienced events at a particular dose were not included in the denominator for that dose group if the event occurred at a dose different than the subject's modal dose.

In the table below, I provide the AE risks by dose from table 24.1 for AEs that occurred in at least 1% of rotigotine subjects and that occurred commonly when compared to placebo subjects.

Treatment Emergent Adverse Events by Dose of Longest Duration, For AEs Occurring in at Least 1% of Rotigotine Subjects and at Least Twice as Common Compared to Placebo Subjects, Pool S1

	Placebo	Rotigotine			
Preferred Term	(n=289)	4.5mg/day (n=104)	9mg/day (n=68)	13.5mg/day (n=223)	18mg/day (n=254)
Application site reactions	13.8% (40)	20.2% (21)	23.5% (16)	44.8% (100)	40.2% (102)
Mouth Dry	1.4% (4)	2.9% (3)	4.4% (3)	0.9% (2)	4.7% (12)
Fever	0.3% (1)	1% (1)	1.5% (1)	1.3% (3)	1.6% (4)
Gait abnormal	0	1.9% (2)	0	3.1% (7)	1.2% (3)
Confusion	0.3% (1)	1.9% (2)	2.9% (2)	1.3% (3)	0.8% (2)
Nausea	14.9% (43)	49% (51)	35.3% (24)	41.3% (92)	30.3% (77)
Vomiting	2.1% (6)	21.2% (22)	7.4% (5)	11.2% (25)	11.4% (29)
Dyspepsia	1.4% (4)	1.9% (2)	2.9% (2)	5.8% (13)	2.8% (7)
Anorexia	1% (3)	1% (1)	2.9% (2)	5.4% (12)	1.2% (3)
Hiccup	0	1% (1)	2.9% (2)	2.2% (5)	1.2% (3)
GE reflux	0	1% (1)	0	2.7% (6)	0.4% (1)
QT increased	0.3% (1)	1% (1)	1.5% (1)	0.9% (2)	0.4% (1)
Hyperglycemia	0.7% (2)	1.9% (2)	0	0.9% (2)	2% (5)
Insomnia	4.8% (14)	8.7% (9)	8.8% (6)	11.7% (26)	9.1% (23)
Dreaming abnormal	0.3% (1)	1% (1)	7.4% (5)	4.9% (11)	2% (5)
Hallucination	0.7% (2)	1% (1)	5.9% (4)	0.9% (2)	2.4% (6)
Sleep attack	0	0	1.5% (1)	1.3% (3)	2% (5)
Pharyngitis	0	1.9% (2)	0	1.3% (3)	2.4% (6)
Rash erythematous	0.7% (2)	3.8% (4)	2.9% (2)	1.8% (4)	2% (5)
UTI	1.4% (4)	3.8% (4)	0	1.3% (3)	4.3% (11)
Urinary incontinence	0.7% (2)	0	0	3.1% (7)	0.8% (2)
Pyuria	0.3% (1)	1.9% (2)	4.4% (3)	0.4% (1)	0.4% (1)

From NDA ISS table 24.1

To address concerns about Schwarz's denominator calculation for the dose stratified risks provided above, the Division requested a dose response analysis that used person time in the denominator of the risk calculation. For this analysis, Schwarz allotted each subject's rotigotine exposure time into the appropriate dose categories and then summed the time in each dose category to arrive at the total duration of exposure for each dose. Schwarz then used the total exposure for each dose as the denominator for the risk calculations. Schwarz provided a table of AE risks by dose for AEs

occurring in at least 5% of all rotigotine subjects. As with the above analysis, there did not appear to be strong evidence of dose response relationships for many of the reviewed AEs. There was relatively little person time for the 4.5 and 9mg/day doses.

Treatment Emergent Adverse Events Rates by Dose, For AEs Occurring in at Least 5% of Rotigotine Subjects, Pool S1

	Placebo	Rotigotine			
	1867 PM	4.5mg/day 319 PM	9mg/day 320 PM	13.5mg/day 1176 PM	18mg/day 1445 PM
Preferred Term	AE Rates per 100 Patient Months (PM)				
Application site reactions	3.9	26.0	9.4	9.4	6.9
Fatigue	1.5	6.9	5.6	0.5	1.0
Dizziness	2.6	15.0	6.3	3.8	2.3
Headache	2.7	13.5	5.9	2.4	1.7
Nausea	4.4	45.1	21.3	6.0	4.4
Vomiting	0.6	11.9	3.1	1.5	2.2
Diarrhea	1.1	1.6	0.3	0.9	0.8
Constipation	0.7	2.8	1.9	1.1	0.8
Dyspepsia	0.3	2.2	1.3	0.9	0.6
Abd pain	0.6	0.6	0.3	0.4	0.4
Back pain	1.1	1.6	1.6	0.7	1.1
Somnolence	3.5	17.6	7.5	5.2	3.3
Insomnia	1.3	5.0	4.1	1.3	1.1
Hallucination	0.1	0.6	1.3	0.4	0.2
URI	1.4	0.3	1.9	1.1	0.9
Coughing	0.7	1.3	0.9	0.9	0.6
Fall	1.4	0.3	0.6	2.2	0.4

From Table 1, 12/23/05 submission

In addition to the dose dependency analyses, Schwarz provided analyses for AEs from pool S1 studies occurring in at least 5% of rotigotine subjects that stratified on the demographic variables of age (<65, >=65), sex, BMI, and race (White, Black, Asian, and other). I provide summary tables with calculated relative risks for age, sex, and BMI below. I do not include Schwarz's tables that stratified by race because there were too few subjects classified as Black (placebo n=4, rotigotine n=5), Asian (placebo n=2, rotigotine n=11) or other (placebo n=15, rotigotine n=34) to allow for meaningful comparisons.

Common Treatment Emergent AEs Occurring in at least 5% of Subjects in Pool S1 Studies, by Age Group

	Age <65			Age >=65		
Preferred Term	Placebo N=164	Rotigotine N=390	RR	Placebo N=125	Rotigotine N=259	RR
Application Site React	13.4% (22)	37.7% (147)	2.8	14.4% (18)	35.5% (92)	2.5
Fatigue	7.3% (12)	9% (35)	1.2	6.4% (8)	5.4% (14)	0.8
Dizziness	9.1% (15)	18.7% (73)	2.1	13.6% (17)	17.4% (45)	1.3
Headache	11% (18)	16.7% (65)	1.5	9.6% (12)	8.9% (23)	0.9
Nausea	18.9% (31)	42.8% (167)	2.3	9.6% (12)	29.7% (77)	3.1

Vomiting	3% (5)	14.4% (56)	4.8	0.8% (1)	9.7% (25)	12.1
Constipation	4.3% (7)	3.8% (15)	0.9	3.2% (4)	7.7% (20)	2.4
Dyspepsia	0	3.6% (14)	-	3.2% (4)	6.9% (18)	2.2
Diarrhea	4.3% (7)	2.3% (9)	0.5	3.2% (4)	6.9% (18)	2.2
Abdominal pain	3% (5)	2.1% (8)	0.7	2.4% (3)	3.1% (8)	1.3
Back pain	4.3% (7)	6.4% (25)	1.5	6.4% (8)	4.2% (11)	0.7
Somnolence	12.2% (20)	24.9% (97)	2.0	20% (25)	24.7% (64)	1.2
Insomnia	6.7% (11)	11.5% (45)	1.7	2.4% (3)	7.3% (19)	3.0
Hallucination	0	1.5% (6)	-	1.6% (2)	2.7% (7)	1.7
Up Resp Tract inf	6.7% (11)	5.4% (21)	0.8	4% (5)	5% (13)	1.25
Coughing	3.7% (6)	3.8% (15)	1.0	4% (5)	2.7% (7)	0.7
Fall	5.5% (9)	3.8% (15)	0.7	10.4% (13)	5% (13)	0.5

From ISS Table 58.1.3

Common Treatment Emergent AEs Occurring in at least 5% of Subjects in Pool S1 Studies, by Sex

	Male			Female		
Preferred Term	Placebo N=164	Rotigotine N=405	RR	Placebo N=125	Rotigotine N=244	RR
Application Site React	14% (23)	37.3% (151)	2.7	13.6% (17)	36.1% (88)	2.7
Fatigue	4.3% (7)	7.9% (32)	1.8	10.4% (13)	7% (17)	0.7
Dizziness	9.1% (15)	19.3% (78)	2.1	13.6% (17)	16.4% (40)	1.2
Headache	6.1% (10)	13.3% (54)	2.2	16% (20)	13.9% (34)	0.9
Nausea	13.4% (22)	35.3% (143)	2.6	16.8% (21)	41.4% (101)	2.5
Vomiting	1.2% (2)	11.1% (45)	9.3	3.2% (4)	14.8% (36)	4.6
Constipation	4.9% (8)	6.4% (26)	1.3	2.4% (3)	3.7% (9)	1.5
Dyspepsia	1.8% (3)	3.7% (15)	2.1	0.8% (1)	3.7% (9)	4.6
Diarrhea	4.3% (7)	3.5% (14)	0.8	3.2% (4)	5.3% (13)	1.7
Abdominal pain	3% (5)	2% (8)	0.7	2.4% (3)	3.3% (8)	1.4
Back pain	4.3% (7)	5.7% (23)	1.3	6.4% (8)	5.3% (13)	0.8
Somnolence	11.6% (19)	26.7% (108)	2.3	20.8% (26)	21.7% (53)	1.0
Insomnia	4.3% (7)	11.6% 947)	2.7	5.6% (7)	7% (17)	1.3
Hallucination	0.6% (1)	3% (12)	5.0	0.8% (1)	0.4% (1)	0.5
Up Resp Tract inf	6.1% (10)	5.7% (23)	0.9	4.8% (6)	4.5% (11)	0.9
Coughing	4.3% (7)	3.7% (15)	0.9	3.2% (4)	2.9% (7)	0.9
Fall	6.1% (10)	2.5% (10)	0.4	9.6% (12)	7.4% (18)	0.8

From ISS Table 58.1.3

Common Treatment Emergent AEs Occurring in at least 5% of Subjects in Pool S1 Studies, by BMI

	18.5-<25			25-<30			>=30		
Preferred Term	PBO N=98	Rotig N=217	RR	PBO N=127	Rotig N=276	RR	PBO N=56	Rotig N=144	RR
Application Site React	13.3% (13)	35% (76)	2.6	16.5% (21)	37.3% (103)	2.3	10.7% (6)	38.2% (55)	3.6
Fatigue	7.1% (7)	5.1% (11)	0.7	5.5% (7)	10.9% (30)	2	10.7% (6)	5.6% (8)	0.5
Dizziness	14.3% (14)	18% (39)	1.3	10.2% (13)	19.9% (55)	2	8.9% (5)	13.2% (19)	1.5
Headache	13.3%	10.6%	0.8	8.7%	15.6%	1.8	10.7%	13.9%	1.3

	(13)	(23)		(11)	(43)		(6)	(20)	
Nausea	20.4% (20)	45.6% (99)	2.2	11.8% (15)	31.5% (87)	2.7	14.3% (8)	35.4% (51)	2.5
Vomiting	4.1% (4)	16.1% (35)	3.9	0.8% (1)	10.5% (29)	13.1	1.8% (1)	10.4% (15)	5.8
Constipat	3.1% (3)	5.1% (11)	1.6	3.9% (5)	6.5% (18)	1.7	5.4% (3)	4.2% (6)	0.8
Dyspepsia	0	2.3% (5)	-	2.4% (3)	4.3% (12)	1.8	1.8% (1)	3.5% (5)	1.9
Diarrhea	5.1% (5)	3.2% (7)	0.6	3.9% (5)	4.7% (13)	1.2	1.8% (1)	3.5% (5)	1.9
Abd pain	5.1% (5)	2.3% (5)	0.5	0.8% (1)	2.9% (8)	3.6	3.6% (2)	2.1% (3)	0.6
Back pain	5.1% (5)	6% (13)	1.2	5.5% (7)	5.8% (16)	1.1	5.4% (3)	3.5% (5)	0.6
Somnolen	14.3% (14)	21.2% (46)	1.5	16.5% (21)	24.3% (67)	1.5	16.1% (9)	30.6% (44)	1.9
Insomnia	3.1% (3)	6.9% (15)	2.2	6.3% (8)	12% (33)	1.9	5.4% (3)	11.1% (16)	2.1
Hallucin	1% (1)	2.8% (6)	2.8	0.8% (1)	2.2% (6)	2.8	0	0.7% (1)	-
URI	6.1% (6)	6% (13)	1	3.9% (5)	4.7% (13)	1.2	8.9% (5)	5.6% (8)	0.6
Coughing	4.1% (4)	2.8% (6)	0.7	3.9% (5)	3.3% (9)	0.8	3.6% (2)	4.9% (7)	1.4
Fall	9.2% (9)	4.1% (9)	0.4	6.3% (8)	4.7% (13)	0.7	8.9% (5)	4.2% (6)	0.5

The <18.5 category not shown due to small number of subjects (rotigotine n=8)
From ISS Table 58.1.6

In addition to exploring the adverse event data for evidence of demographic interactions, Schwarz provided in depth analyses for selected AEs including application site reactions and events presumed drug related due to the expected AE profile based on rotigotine's pharmacological class (dopamine agonist). Schwarz referred to these AEs as AEs of interest. The discussion of these AEs followed the organ system classification format. In the following sections I summarize Schwarz's presentations of these events.

Application site disorder
Schwartz commented that application site reactions are common with transdermal patch medications and cited published articles describing the risks for such reactions with nitroglycerin (10-75%), fentanyl (45-49%), nicotine (53%), and clonidine (47%).

For all early-stage PD phase II/III trials in the NDA (pool S3), Schwartz reported that 38% (383/1017) of rotigotine subjects experienced application site reactions. Twenty-three early-stage PD rotigotine subjects (2.3%, 23/1017) experienced application site reactions that were rated as severe (Summary of Clinical Safety, p.112). The reported AE terms for these 23 events included reddening/erythema and itching. Three of these 23 events were considered SAEs and 18 subjects discontinued for the event. Nineteen of the 23 severe reactions had an outcome of resolved or completely recovered, two events had outcomes of ongoing, one event had an outcome of not yet

recovered and one event had an outcome of resolved with sequelae. Through the safety update, 5.2% (57/1093) of early-stage PD rotigotine subjects discontinued for application site reactions (Safety Update Tale 5.1, pp 800-7).

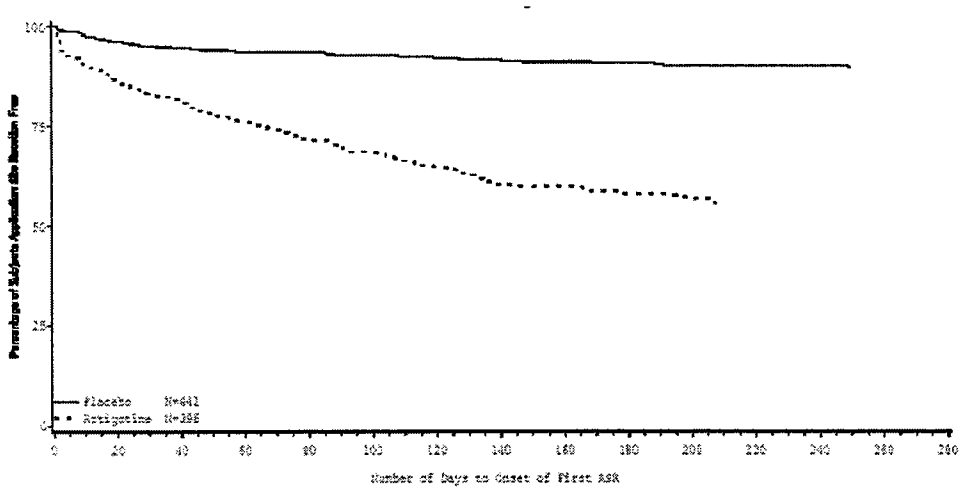
Schwartz reports that in the early-stage PD controlled trials in the NDA (pool S1), 37% (239/649) of rotigotine and 14% (40/289) of placebo treated subjects experienced application site reactions (summary of Clinical Safety, p.84). Schwartz more closely examined these events in two early-stage PD controlled trials (SP512DB and SP513DB). Schwartz focused on these two trials because the protocols directed that patch sites be rotated among the abdomen, thigh, hip, flank, shoulder, and upper arm, similar to the recommendations in their proposed labeling. Study SP506 was not included in the analysis because the protocol for SP506 specified that patches be applied only to the upper abdomen. In their analyses, Schwartz combined the placebo and ropinirole treatment randomized groups since both groups received dummy patches. For trials SP512DB and SP513DB, applications site reactions were reported for 40% (160/396) of rotigotine subjects compared to 9% (41/441) of placebo/ropinirole subjects. The following table summarizes characteristics of application site reaction from studies SP512DB and SP513DB.

Summary statistics for subjects in Pool S4 with application site reactions during treatment (subjects with at least 1 application site reaction)

Parameter	Placebo N=41 n (%)	Rotigotine N=160 n (%)
Intensity of application site reaction		
Mild	40 (98)	127 (79)
Moderate	1 (2)	44 (28)
Severe	0	6 (4)
Application site reaction reported as SAE	0	3 (2)
Outcome of application site reaction		
Completely recovered	37 (90)	122 (76)
Recovered with sequelae	0	1 (1)
Not yet recovered	0	8 (5)
Deterioration	0	3 (2)
Ongoing[a]	5 (12)	43 (27)
Entered open-label extension		
Yes	34	103
No, because		
Withdrew due to application site reaction	0	27
Withdrew due to other reasons	7	18
Completed maintenance period, but declined	0	12

SAE=serious adverse event
NOTE: Subjects may have experienced more than one application site reaction in different categories and therefore may be counted more than once for intensity and outcome.
a Ongoing and not completely recovered application site reactions were followed by the investigator until resolved or stable or were re-assessed if the subject entered the open-label extension trial.
Data source: ISS Table 64.1

Within the two included trials, the median time to onset of an application site reaction was 44 days (mean 60 days, range 1-207 days) and most subjects were administered a dose of either 13.5mg/day or 18mg/day at the time of the event, although the titration design of these studies complicates interpretation of risk by dose. Schwartz noted that when the data for study SP506 (abdominal patch site) were included, the median time to onset dropped to 28 days suggesting that patch rotation may delay application site reactions. Schwartz provided a Kaplan Meier curve for application site reactions in studies SP512DB and SP513DB, which showed the risk among rotigotine subjects was increased early and the relative risk compared to placebo/ropinirole continued to increase over the duration of the study. That curve is provided below.



Risk for application site reactions did not appear to be influenced by age or gender. In the early-stage PD controlled trials (pool S1) there was little difference in relative risk for application site reactions when comparing rotigotine subjects <65 years (RR 2.9, rotigotine 38% [147/390]; placebo 13% [22/164]) to those >=65 years (RR 2.6, rotigotine 36% [92/259]; placebo 14% [18/125])[Summary of Clinical Safety, ISS Table 58.1.3, pp 2239-46]. The relative risk for application site reactions was similar for males (RR 2.6, rotigotine 37% [151/405]; placebo 14% [23/164]) and females (RR 2.6, rotigotine 36% [88/244]; placebo 14% [17/125])[Summary of Clinical Safety Table 58.1.4, pp 2247-50].

The risks for application site reactions were similar to the early-stage PD studies in an advanced-stage PD study and slightly lower in a restless leg study. In study SP650DB, a controlled trial in advanced-stage PD, the risk for application site reactions among rotigotine subjects were 36% (43/118) for 18mg/day and 46% (51/111) for 27mg/day compared to 13% (16/120) for placebo (Safety update p.121). In the restless leg controlled trial SP709 the risk for application site reactions among rotigotine subjects was 18% (50/285) and 2% (1/55) in placebo subjects (Safety Update, p.138). This observed lower risk in the RLS trial could be due to differences in trial duration. The treatment duration in RLS study SP709 was 7 weeks whereas the treatment durations in PD trials were 38 weeks in SP650 DB, 37 weeks in SP513 Part I, 27 weeks in SP 5123 Part I, and 12 weeks in SP506.

Schwartz noted that two phase I studies were performed to examine skin irritation and sensitization potential. In study SP673, Schwartz reported that none of the 221 subjects showed sensitization reactions following a single 48 hour application of the rotigotine or placebo patch. In this study, subjects were exposed to a rotigotine (1.125mg/patch) or placebo patch 3 times weekly for 3 weeks, followed by a rest phase, and then a challenge phase of 48 hours. Study SP629 found, following repetitive application to the same site in 40 subjects, higher measures of irritation for the rotigotine patch compared to placebo or the low irritancy control (0.9% NaCl) and slightly lower measures of irritation for rotigotine compared to the high irritancy control (sodium lauryl sulfate). The same study found lower measures of irritation with rotigotine when the patch site was rotated. The investigators reported that four subjects had reactions that could be indicative of sensitization (AEs reported as contact eczema on multiple patch application sites). After recovery, 3 of these subjects were re-exposed for 2 days. Skin reactions were assessed 96 hours after patch removal and 2 of the subjects developed type-IV contact dermatitis (clinical diagnosis supported by skin biopsies) at the rotigotine but not the placebo patch sites. The third subject had a reaction that was difficult to differentiate between allergic and toxic contact dermatitis.

Schwartz reports risks of application site reactions with rotigotine that are similar in frequency to the risks observed with other transdermal patch medications, although they do not present data from studies that directly compare such risks. The overall risk of application site reaction with rotigotine was approximately 40%, about 3-4 times the risk in the placebo/dummy patch group. Application site reactions led to discontinuation of approximately 5% of rotigotine subjects and just over 2% of rotigotine subjects experienced severe reactions compared to none in the placebo group. Schwartz provided evidence that patch rotation may delay appearance of these reactions although the recommendation to not reapply to a site within 14 days complicates use. Many of the reactions resolved with patch removal. One study documented sensitization in 2/40 subjects.

Autonomic nervous system disorders
Schwarz provided additional information about orthostatic hypotension and syncope AEs, which they identified as class effects of dopamine agonists. Schwarz reviewed the verbatim and preferred terms to identify all AEs suggestive of orthostatic hypotension. Schwarz provided a listing of these events and the listing included terms for postural hypotension, dizziness, vertigo, syncope, accident NOS, and fall (Summary of Clinical Safety, p.116). For the S1 pool of early-stage PD controlled trials, Schwarz reported that the risk for events suggestive of orthostatic hypotension was similar for the rotigotine (5%, 29/649) and placebo (4%, 12/228) treatment groups (Summary of Clinical Safety, p.116). Schwarz noted that the risk for syncope was similar for rotigotine (1%, 7/649) and placebo (1% (2/289) subjects and was less than the risk seen among ropinirole (3%, 7/228) subjects.

Cardiovascular events
Schwarz provided information about edema and hypertension AEs. Schwarz identified extremity edema as a class effect of dopamine agonists and provided additional analyses of these AEs. Schwarz combined events of edema dependent, edema peripheral, and edema legs for this analysis. Schwarz reported that the risk for extremity edema events for ropinirole was 7% (43/649) compared to 6% (16/289) for placebo and 4% (10/228) for ropinirole (Summary of Clinical Safety, p. 117). None of these events were SAEs, and 2 rotigotine subjects discontinued for edema AEs compared to no placebo or ropinirole subjects.

Schwarz examined the risk for hypertension (hypertension, hypertension aggravated) AEs. The risk for hypertension related AEs was 4% (23/649) for rotigotine, 3% (8/289) for placebo, and 7% (15/228) for ropinirole. Hypertension was an SAE for one rotigotine and one ropinirole subject but no subjects discontinued or had study medication dose reduction for a hypertension related event (Summary of Clinical Safety, p. 118).

Central Nervous System Events
Schwarz provided additional information about dyskinesia, convulsion and headache. Schwarz identified dyskinesia as a class effect of dopamine agonists. To investigate dyskinesia risk further, Schwarz grouped the following events dyskinesia, hyperkinesia, and muscle contractions involuntary. The risk for this pool of events was 3% (19/649) for rotigotine, 2% (5/289) for placebo, and 1% (2/228) for ropinirole subjects. No rotigotine subjects had an SAE due to a dyskinesia related AE. No subjects discontinued or had trial dose reduction for one of the dyskinesia related AEs (Summary of Clinical Safety, pp. 118-119).

One rotigotine and no placebo or ropinirole subjects in pool S1 trials experienced an AE of convulsions (Summary of Clinical Safety, p. 119).

In pool S1 studies, the risk for headache AEs was 14% (88/649) for rotigotine compared to 10% (30/289) for placebo and 9% (20/228) for ropinirole. One rotigotine subject experienced a headache that was an SAE. Headache led to discontinuation of 3 (<1%, 3/649) rotigotine subjects and 1 (<1%, 1/289) placebo subject. Headache led to study dose reduction for 4 (<1%, 4/649) rotigotine subjects and 1 placebo subject (<1%, 1/289) (Summary of Clinical Safety, p. 119).

Endocrine events
Schwarz noted that dopamine agonists cause decreased prolactin. No AEs related to prolactin were reported in pool S1 studies (Summary of Clinical Safety, p. 120).

Gastrointestinal events
Schwarz examined the AE risk data from pool S1 studies for nausea, vomiting, and abdominal pain. Nausea was reported as an AE for 38% (244/649) of rotigotine subjects, 15% (43/289) of placebo subjects and 36% (82/228) of ropinirole subjects. For rotigotine subjects, nausea was reported most frequently during titration and at the lowest dose (4.5mg/day). The median time to onset for nausea was 18 days for rotigotine compared to 32 days for placebo. The median duration of first nausea adverse event was 5 days for rotigotine and 4 days for placebo. Nausea was not reported as an SAE in the pool S1 trials, but led to discontinuation of 13 rotigotine subjects (2%, 13/649), 6 ropinirole subjects (2.6%, 6/228) and no placebo subjects, and dose reduction in 40 rotigotine subjects (6%, 40/649) and 2% (5/289) placebo subjects (Summary of Clinical Safety, p.120). Vomiting was reported as an AE for 13% (81/649) of rotigotine subjects, 2% (6/289) of placebo subjects and 11% (25/228) of ropinirole subjects. For rotigotine subjects, vomiting was reported at the highest frequency during titration, and at the lowest dose (4.5mg/day). The median time to onset for vomiting was 19 days for rotigotine subjects compared to 37 days for placebo subjects. The median duration of first vomiting event was 1 day for both rotigotine and placebo subjects. Vomiting was reported as an SAE for one rotigotine subject in the pool S1 trials. Vomiting led to discontinuation of eight rotigotine subjects (1%, 8/649), 2 ropinirole subjects (0.9%, 2/228), and no placebo subjects,

and dose reduction in 20 rotigotine subjects (3%, 20/649) and no placebo subjects (Summary of Clinical Safety, p.120).

In pool S1 studies, the risk for abdominal pain was similar for rotigotine (3%, 16/649) and placebo subjects (3%, 8/289). Abdominal pain was reported as an SAE for 2 rotigotine subjects (<1%, 2/649) and no placebo subjects. One rotigotine subject discontinued and one had study medication dose reduced for abdominal pain compared to no placebo subjects.

Heart Rate and Rhythm events
Schwarz reported no difference in Heart Rate and Rhythm disorder AE risk for rotigotine (6%, 39/649) and placebo (6%, 18/289) subjects in pool S1 studies. Schwarz also compared risks for heart rate and rhythm disorders for which the intensity was rated as severe. One rotigotine subject (<1%, 1/649) and one placebo subject (<1%, 1/289) had a severe heart rate and rhythm disorder AE. The rotigotine subject experienced atrial fibrillation and QT increased and the placebo subject experienced QT increased. Schwarz noted that there was one sudden death[4] in controlled and open label (pool S3) early-stage PD studies and that this event occurred in a subject treated with rotigotine (Summary of Clinical Safety, pp. 122-123).

Hematologic events
Schwarz did not identify differences in risk by treatment for hematologic AEs in pool S1 studies (Summary of Clinical Safety, p.123).

Liver and Biliary system events
Schwarz did not identify differences in risk by treatment for liver and biliary system AEs in pool S1 studies (Summary of Clinical Safety, p.124).

Metabolic/Nutritional events
Schwarz identified neuroleptic malignant syndrome as an event that can occur following abrupt changes in the dose of dopamine agonists. In the pool S1 studies, Schwarz found no events of neuroleptic malignant syndrome or rhabdomyolysis (Summary of Clinical Safety, p.124). However, CPK was not routinely measured in the clinical trials, so asymptomatic elevations of CPK were not identifiable.

Musculoskeletal events
Schwarz conducted an analysis of adverse events related to musculoskeletal pain. For this analysis they included events of myalgia, skeletal pain, back pain, leg pain, arthralgia, and events coded to the term pain that were suggestive of musculoskeletal pain. For the pool of these musculoskeletal pain events, Schwarz reported a risk of 14% (88/649) for rotigotine, 16% (46/289) for placebo, and 11% (26/228) for ropinirole (Summary of Clinical Safety, pp.124-5).

Myocardial, Endocardial, Pericardial, and Valve events
Schwarz reported that no events of pleural effusion, endocardial fibrosis, retroperitoneal fibrosis, mediastinal fibrosis, myocardial fibrosis, pulmonary fibrosis, or pleural fibrosis were observed in the

[4] See section 7.1.1 for description of sudden death case.

S1 pool of studies (Summary of Clinical Safety, pp.125-6). A comprehensive review of possible fibrosis events is presented below in section 7.1.6.

Neoplasm events
Three rotigotine (<1%, 3/649) and two placebo (1%, 2/228) subjects had neoplasm related AEs during pool S1 studies. The neoplasm events for the rotigotine subjects were scalp lump, neoplasm skin lesion, and lump lower right leg (Summary of Clinical Safety, p.126).

Psychiatric events
Schwarz provided an analysis of psychiatric events that they termed "psychotiform" reactions. This analysis included the following events: confusion, depersonalization, hallucination, paranoid reaction, and psychosis. Schwarz reported that 4% (25/649) of rotigotine subjects experienced psychotiform reactions compared to 1% (3/289) of placebo subjects and 8% (19/228) of ropinirole subjects. Hallucination was the event most commonly reported of all the psychotiform reactions. Schwarz noted that 2% of rotigotine subjects (13/649) reported hallucinations compared to <1% (2/289) of placebo subjects and 6% (13/228) of ropinirole subjects. No rotigotine subjects in pool S1 studies experienced hallucinations that were SAEs. One rotigotine and no placebo subjects discontinued for hallucinations and two rotigotine subjects and no placebo subjects had their study medication dose reduced for hallucinations (Summary of Clinical Safety, p.127).

Genitourinary events, Resistance mechanism[5] events, and Respiratory events
Schwarz did not find differences in risk for events classified to these systems (Summary of Clinical Safety, p.128).

Secondary Term events
Schwarz provided information about fall and accident events. Schwarz reported that the preferred term fall captured verbatim terms of fall with no additional injury or fall associated with skin laceration, abrasion, or pain. Schwarz concluded that these events were not suggestive of orthostatic hypotension. Fall was reported by 4% (28/649) of rotigotine subjects and 8% (22/289) of placebo subjects. Two rotigotine and one placebo subject experienced fall SAEs. One placebo subject discontinued following a fall and no subjects had their study drug dose reduced for falls (Summary of Clinical Safety, p.128).

Schwarz reported that the preferred term accident NOS captured events such as abrasions, lacerations, fracture, hematoma, joint sprain, and head and limb injuries possibly suggestive of a fall. Accident NOS was reported for 5% (30/649) of rotigotine subjects and 4% (10/289) of placebo subjects. Seven patients had accident NOS events (3 placebo, 2 ropinirole, and 2 rotigotine) that occurred on the same day as a fall event. Two patients had accident NOS events that occurred on the same day as syncope events, and one patient had an accident NOS event on the same day as a sleep attack (all 3 rotigotine subjects).

[5] Included AEs coded to the preferred terms infection (including bacterial, viral, fungal) and herpes zoster and herpes simplex.

Skin/Appendage events
Aside from application site reactions, there was little difference in risk by treatment for skin related AEs in pool S1 studies. Schwarz reported that 3% (16/649) of rotigotine and 3% (9/289) of placebo subjects experienced rash AEs. In addition, 2% (15/649) of rotigotine and 1% (2/289) of placebo subjects experienced rash erythematous AEs. Two percent (12/649) of rotigotine and 1% (4/289) of placebo subjects experienced pruritis AEs. Pruritis and rash erythematous SAEs were each reported by one rotigotine subject (Summary of Clinical Safety, pp.131-2).

Special Senses, Urinary system, and Vascular Extracardiac events
Schwarz did not find differences in risk for events classified to these systems (Summary of Clinical Safety, p.132).

Vision
Schwarz identified vision abnormalities as associated with the use of dopamine agonists. Schwarz summarized risks for the AE vision abnormal (included events such as flashing lights, blurred vision, floaters, distortions, and sensitivity) in pool S1 studies. Three percent (19/649) of rotigotine and 1% (1/289) of placebo subjects experienced a vision abnormal AE. No subjects had vision abnormalities reported as SAEs.

Falling Asleep During Activities of Daily Living
Schwartz examined sleep related adverse events by individually reviewing somnolence, insomnia, and sleep attack AEs.

Somnolence
Schwartz noted that in pool S1 studies, somnolence was reported as an AE for a higher percentage of rotigotine (25%, 161/649) and ropinirole (29%, 67/228) subjects compared to placebo subjects (16%, 45/289). The median time to onset for somnolence AEs in these studies was shortest for rotigotine (22 days) followed by ropinirole (39 days) and placebo (50 days). In the pool S1 studies, one ropinirole somnolence event was an SAE compared to none for rotigotine or placebo. Schwartz reported that 0.6% (4/649) of rotigotine subjects, 1.3% (3/228) of ropinirole subjects, and no placebo subjects (0/289) discontinued for somnolence AEs (ISS Table 53.1). Schwartz also noted that 2.2% (14/649) of rotigotine subjects, 3.5% (8/228) of ropinirole subjects, and 1% (3/289) of placebo subjects had their study medication dose reduced because of somnolence AEs (ISS Table 57.1). One percent of rotigotine (1%, 7/649) and ropinirole (1%, 2/228) subjects and no placebo patients had somnolence AEs that were rated as severe by investigators (Summary of Clinical Safety, p.133).

Schwartz provided tables that stratified somnolence risk by demographic factors. In the following table, I provide the risks and relative risks compared to placebo stratified by age and sex.

	Rotigotine	Placebo	Relative Risk
Age <65	24.9% (97/390)	12% (20/164)	2.08
Age >=65	24.7% (64/259)	20% (25/125)	1.24
Male	26.7% (108/405)	11.6% (19/164)	2.3
Female	21.7% (53/244)	20.8% (26/125)	1.04

From ISS Tables 58.1.3 and 58.1.4

The table demonstrates that rotigotine subjects <65 years old and males had a higher relative risk for somnolence. A majority of the observed difference in relative risk was due to differences in risk among placebo subjects.

For early-stage PD subjects treated with rotigotine in RCTs and open label trials (pool S3) the risk for somnolence AEs was 23.9% (243/1017) (ISS Table 23.3). None of these events were SAEs (ISS Table 45.2).

Insomnia
In pool S1 studies, 10% (64/649) of rotigotine subjects had AEs of insomnia compared to 6% (14/228) of ropinirole subjects and 5% (14/289) of placebo subjects. No insomnia AEs met the criteria for SAEs. Schwartz reported that 0.8% (5/649) of rotigotine subjects and 0.4% (1/228) of ropinirole subjects but no placebo subjects discontinued from pool S1 studies for insomnia (ISS Table 53.1). One rotigotine subject (0.2%, 1/649) and no ropinirole or placebo subjects had their study medication dose reduced for insomnia (ISS Table 57.1). One percent of rotigotine (1%, 5/649) and <1% of placebo (1/228) subjects had insomnia AEs that were rated as severe by investigators (Summary of Clinical Safety, p.134).

Schwartz provided tables that stratified insomnia risk by demographic factors. In the following table, I provide the risks and relative risks compared to placebo stratified by age and sex.

	Rotigotine	Placebo	Relative Risk
Age <65	24.9% (97/390)	6.7% (11/164)	3.7
Age >=65	7.3% (19/259)	2.4% (3/125)	3.0
Male	11.6% (47/405)	4.3% (7/164)	2.7
Female	7.0% (17/244)	5.6% (7/125)	1.25

From ISS Tables 58.1.3 and 58.1.4

The relative risks for insomnia were similar for the two age groups. Male subjects had a higher relative risk for insomnia than females.

For early-stage PD subjects treated with rotigotine in RCTs and open label trials (pool S3) the risk for insomnia AEs was 10.5% (107/1017) (ISS Table 23.3). None of these events were SAEs (ISS Table 45.2).

Sleep attacks
Schwartz noted that sleep attacks, the sudden onset of sleep without warning, were AEs of special interest per protocols during the development program. In pool S1 studies, no placebo subjects experienced sleep attack AEs compared to 1.4% (9/649) of rotigotine subjects and 1.8% (4/228) of ropinirole subjects. In pool S1 studies, 2 rotigotine subjects and no ropinirole subjects experienced sleep attack SAEs. One rotigotine and one ropinirole subject discontinued from pool S1 studies for sleep attack AEs. Two ropinirole and no rotigotine subjects had their study medication dose reduced following sleep attack AEs. One ropinirole subject and no rotigotine subjects had sleep attack AEs that were rated severe (Summary of Clinical Safety, p.134).

For early-stage PD subjects treated with rotigotine in RCTs and open label trials (pool S3) the risk for sleep attack AEs was 1.3% (13/1017) (ISS Table 23.3). Four of these events (0.4%, 4/1017) were SAEs (ISS Table 45.2). The narratives for the sleep attack SAEs were reviewed above. As noted previously most of these sleep attack SAEs occurred while driving.

7.1.6 Less Common Adverse Events

Schwarz did not provide a general discussion of less common AEs. I read the AE listings from each of the different safety grouping pools to identify less commonly occurring but potentially important AEs. Specifically, I reviewed data from phase II/III trials for early-stage PD (pool S3, n=1093 data from SU), advanced PD (trials 650 DB and OL, data from SU; trials 511, 533, and 591, data from study reports in the NDA, n=589) and RLS (trials 709 and 710, data from SU; trials 628, 666, data from study reports in the NDA, n=389). Among rotigotine treated subjects, I found no AEs suggestive 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 (1/256).

Fibrosis events

In addition to the analysis of fibrosis AEs provided above, Schwarz responded to a request for a more in depth analysis of their safety database for possible cases of fibrosis. The division requested that Schwarz search for events potentially associated with fibrosis or fibrotic complications of the respiratory, cardiovascular, gastrointestinal, or urogential body systems. In a 6/24/05 submission, Schwarz responded to the division's request.

Schwarz described their approach to the analysis for fibrosis events. Schwarz included data from early-stage PD, advanced PD, and RLS studies. They excluded data from seven short duration trials. Three Schwarz physicians reviewed the AE listings which included data through the Safety Update. The reviewers identified the following eleven preferred terms with a potential association with fibrosis: heart murmur, heart valve disorders, intestinal obstruction, mitral insufficiency, pleural effusion, pneumonia, respiratory disorder, respiratory insufficiency, hydronephrosis, and urethral disorder. All AEs coded to these preferred terms were identified and the individual cases were reviewed. The reviewers excluded cases of pneumonia that appeared infectious in nature and the urethral disorder which was deemed not relevant as a fibrotic complication.

The Schwarz reviewers identified 13 potential fibrosis or fibrotic complication events in 11 study subjects. Two of the 11 subjects received only placebo (events bilateral hydronephrosis/pleural effusion, heart murmur). The remaining 10 events occurred in 9 subjects who received rotigotine. Seven of these events were heart murmur or heart valve disorders and there were no cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, or pleural thickening. The following table summarizes these events in rotigotine subjects.

Subjects who Experienced AEs with a Potential Link to Fibrosis of Fibrotic Comlications

Patient ID	AE Preferred Term/Verbatim Term	Concomitant medications that enhance dopaminergic tone
SP650OL/11601	Intestinal obstruction/Bowel obstruction	Carbidopa/levodopa

SP650DB/13902	Heart murmur/Systolic murmur 3/5	Carbidopa/levodopa
SP512OL/13702	Heart murmur/S3 gallop	None
SP512OL/14003	Pneumonitis/Pneumonitis	None
SP506/1031	Heart murmur/Systolic murmur	None
SP506/1561	Heart murmur/Grade I blowing systolic murmur	None
SP512OL/10404	Heart murmur/VI systolic ejection murmur	None
SP513OL/103703	Mitral insufficiency/ Mitral regurgitation	Selegiline
SP512OL/10701	Heart valve disorders/Mild mitral valve prolapse; Mitral insufficiency/Moderate mitral valve regurgitation	None

From 6/24/04 submission, pp.10-11

Schwarz concluded that there "is no reasonable likelihood that these AEs may have been caused or exacerbated by treatment rotigotine."

Schwarz provided narratives for each of the potential fibrosis/fibrotic complication events and also provided reviewer comments about the potential relationship between the events and rotigotine. I read the narratives and Schwarz's comments. Subjects 650DB/13902, SP506/00210, and SP506/06921 developed systolic murmurs and Schwarz did not consider the events related to rotigotine because of the short duration of exposure (176 days, 55 days, 72 days, respectively). Subject SP512OL/10404 developed a I/VI systolic murmur and the reviewers felt that this was most likely a physiological heart murmur without clinical importance. Subject SP512OL/10701 was diagnosed with mitral valve prolapse and mitral insufficiency during a workup for TIA and the reviewers commented that there was no reasonable likelihood that these events were the result of fibrosis. Subject SP513OL/103703 was diagnosed with mitral insufficiency and the reviewers commented that it is unlikely that the event was due to rotigotine because of the short duration of exposure (91 days). For subject SP512OL/13702, Schwarz noted that this subject who was diagnosed with an S3 gallop has a history of irregular heart beat and that irregular heart beats are not symptoms of fibrosis. Subject SP512OL/14003 had an event of pneumonitis that resolved following antibiotic treatment and the reviewers felt this event was most likely a bacterial infection and not fibrosis

Schwarz found no cases of retroperitoneal fibrosis, pulmonary fibrosis, pleural fibrosis or hydronephrosis in their database of rotigotine treated subjects. There were occasional cases of patients with newly documented heart murmurs but there is little useful information about these events because they generally were not investigated further by echocardiography.

The small number of potentially fibrotic events is somewhat but not completely reassuring for at least two reasons. First, the rotigotine studies did not include monitoring for fibrosis cases, potentially limiting the ability to identify cases. Second, if development of fibrotic complications is a process requiring a long interval of time and or duration of exposure, then the ability to observe these events would be limited because data on long term rotigotine use are relatively small.

Compulsive Gambling and or Eating, Hypersexuality
Recently, use of dopamine agonists has been linked to compulsive behaviors such as gambling, overeating, and hypersexuality. I reviewed the listing of AEs for pool S3 through the Safety Update

(SU table 68.2) and found no AEs suggestive of compulsive gambling, compulsive eating, hypersexuality, or any other compulsive behavior. The study protocols did not include specific questions about compulsive behaviors. Because compulsive behaviors may not be recognized as adverse events, the sensitivity to detect such events in the absence of specific questioning is suspect.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Laboratory assessments were performed on blood and urine samples obtained at protocol-defined visits within each trial. Samples for laboratory assessments in clinical trials SP512DB and SP513DB were collected pre-treatment, at the commencement of dose escalation, at the commencement of the maintenance phase, after 12 and 24 weeks of the maintenance phase, and at the safety follow-up assessment after the end of treatment for subjects not continuing into the open-label phases; open-label subjects were monitored while taking rotigotine. These laboratory assessments were also to be performed in the event that a subject was prematurely withdrawn from the trial but it is not clear whether sampling occurred before or after (and how soon after) treatment ended (whether the patient finished the trial or discontinued early). Blood samples for the measurement of serum prolactin levels (assessed only in SP512DB) were taken at the commencement of dose escalation; at the commencement of the maintenance phase; after 8, 16, and 24 weeks on maintenance treatment; and at the safety follow-up assessment. Samples for laboratory assessments were collected at all scheduled visits in SP506, including the safety follow-up visit and premature withdrawal visit.

SP534 Parts 1 and 2 collected samples each week and at any time a subject terminated early from the trial. Clinical laboratory samples in SP535 were collected from each subject during screening, weekly during dose titration and maintenance, at safety follow-up; and at any time a subject discontinued from trial. Prolactin samples for analysis were collected weekly during treatment, or at the premature termination visit. SP540 collected samples during screening, dose escalation, maintenance, and at the safety follow-up visit and at any time a subject discontinued early from the trial.

The laboratory analyses listed below were collected in all studies except where noted:

Hematology: red blood cell count, white blood cell count, WBC differential, platelet count, hemoglobin and hematocrit.

Blood chemistry: sodium, potassium, chloride, carbon dioxide (Phase 2 studies only), albumin, GGT, SGOT (AST), SGPT (ALT) glucose, calcium, alkaline phosphatase, thyroxine (SP506 only), total cholesterol (Pool S1 only), total protein, BUN, inorganic phosphorus, total bilirubin, uric acid (SP512 and SP513 [Pool S5] only) and creatinine

Urinalysis: pH, specific gravity (Phase 2 only), microscopic (cells, casts, etc – Phase 2 only) color/appearance, glucose, protein and blood

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The principal safety analyses were conducted on the S1 pool, consisting of the double-blind phases of the SP506, SP512 and SP513 studies. The laboratory data are presented as means, standard deviations, medians, minimum values, and maximum values for baseline, end of treatment, maximum value during treatment and minimum value during treatment. Change from baseline values (mean, median, minimum, and maximum change from baseline) are presented for end of treatment, maximum value during treatment and minimum value during treatment. For these analyses, the combined rotigotine group (all doses of rotigotine combined) is compared to placebo and to ropinirole (the active control in SP513DB). For end of treatment analyses, the last available measurement during the considered period was used. In addition, more detailed analyses of means, standard deviations, medians, minimum, maximum, and change from baseline values by modal dose of rotigotine compared to placebo at end of titration and at Months 3, 6, and 9 of maintenance were presented to examine the data for any trends over time. For these analyses, the ropinirole arm of SP513DB was not included. For Pool S1, the titration phase was 4 weeks for SP506, 3 weeks for SP512 and 13 weeks for SP513 and the length of the maintenance phase was approximately 2 months for SP506, up to 6 months for SP512DB, and up to 9 months for SP513DB.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Extensive tables listing the analyses described above are attached to the application but no overview by the sponsor is given by either narrative or table. With the exception of prolactin, the sponsor describes all laboratory measurements as lacking any clinically relevant trends or changes from baseline. Prolactin levels in the SP512DB study were, as expected, significantly lower with rotigotine, averaging approximately 2 ng/mL lower with the 13.5 mg patch than what was observed for placebo.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The sponsor describes all of the chemistry and urinalysis results as being without any clinically relevant shifts from baseline or differences in the incidence of abnormal values. For hematology, they describe differences for Pool S1 as summarized in Reviewer's Table 7.1.7.3.2

Reviewer's Table 7.1.7.3.2:
Proportion of Subjects in Pool S1 with Initial Normal Values Reporting Abnormally Low Hematology Values at Any Subsequent Visit

	Placebo	Rotigotine	Ropinirole
Hematocrit	6%	9%	9%
Hemoglobin	5%	8%	8%
RBC Count	4%	7%	4%
Monocyte Count	6%	9%	9%

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

CTD Section 2.7.4.7.3 presents laboratory normal ranges and ranges for markedly abnormal values for the Pool S1 and S6 studies. In the majority of cases, the criteria for markedly abnormal results are different from the criteria used in the submitted laboratory data set. As such, the analyses performed by the sponsor cannot be interpreted because it is not clear whether the criteria for markedly abnormal values are those listed in the Summary of Clinical Safety or those given in the laboratory data set. This reviewer performed his own analyses using the laboratory data set for the S1 and S6 Pools with the criteria for marked abnormality given in the data set. These criteria are listed in Reviewer's Appendix 1. The incidence of marked abnormalities was low and similar in the placebo and rotigotine groups with exceptions shown in Reviewer's Table 7.1.7.3.3.1.

Reviewer's Table 7.1.7.3.3.1:
Incidence of Marked Abnormalities[c] at Any Treatment Visit of Selected Laboratory Tests in Pool S1 and Subjects originally assigned to Rotigotine in Pool S6

	Placebo		Rotigotine		Ratio
	Number[a]	%[b]	Number[a]	%[b]	
SGPT (ALT)	0	0.00%	4	0.12%	inf
Hematocrit	1	0.11%	16	0.51%	4.49
BUN	1	0.11%	10	0.31%	2.81
Potassium	1	0.11%	7	0.22%	1.96
WBC Count	2	0.22%	13	0.41%	1.83
Hemoglobin	4	0.45%	24	0.76%	1.69
Platelet Count	1	0.11%	6	0.19%	1.69
Monocytes	1	0.11%	4	0.13%	1.13

[a]Number of abnormal results [b]Percentage of results that are markedly abnormal
[c]The criteria for marked abnormalities are listed in Appendix 1.

The sponsor did not describe in any detail any subjects with markedly abnormal biochemistry or urinalysis results. Several subjects with marked hematological abnormalities are described but only with narrative descriptions of changes in these values. No additional information is provided. Full clinical narratives including medical history, other medications and laboratory values are necessary to evaluate all of the rotigotine subjects reporting marked abnormalities of the laboratory tests listed in Table 7.1.7.3.3.1. These subjects with the abnormalities observed are listed in Reviewer's Appendix 2.

7.1.7.4 Additional analyses and explorations

The measures of central tendency presented by the sponsor are limited in the number of points of observation and the absence of statistical testing. The pooling of studies can also be misleading, given the different protocols and proportions of subjects in treatment groups. These analyses do not detect trends over time.

In order to more completely capture information on laboratory tests a mixed effects linear model was used to look for differences in trends over time between subjects receiving rotigotine and those

receiving placebo. The model examines linear trends in individual subjects, nesting subjects within trials and treating both as random effects. The primary statistical test determines whether there is a significant difference in the slope and intercept of trends over time between subjects receiving rotigotine and those receiving placebo. The results for the 35 laboratory studies given in the sponsor's dataset using the S1 pool plus the open label extensions for subjects originally assigned to rotigotine are given in Reviewer's Table 7.1.7.4.1.

Given the large number of statistical tests, only hemoglobin (echoed by hematocrit and red blood cell count) and albumin (echoed by total protein and calcium) appear to be significant and were analyzed in greater detail. Some note may be given as well to the borderline significance of SGPT, which may reflect the presence of marked outliers noted in the preceding section.

It should be noted that the sponsor's laboratory data set reports hemoglobin levels in units of g/L rather than the conventional g/dL. The hemoglobin levels presented here will, therefore, appear nominally ten times greater than if conventional units were used.

Reviewer's Table 7.1.7.4.1:
Difference in Changes from Baseline in Laboratory Test Results between Rotigotine and Placebo (Mixed Effects Model)

Test	p value
Albumin	0.003
Alkaline Phosphatase	0.407
Basophils	0.478
Basophils Abs	0.146
Eosinophils	0.344
Eosinophils Abs	0.451
Lymphocytes	0.402
Lymphocytes Abs	0.184
Monocytes	0.524
Monocytes Abs	0.436
Neutrophils	0.226
Neutrophils Abs	0.818
Bicarbonate	0.686
BUN	0.177
Calcium	0.075
Chloride	0.218
Creatinine	0.888
GGT	0.357
Glucose	0.387
Hematocrit	0.037
Hemoglobin	$<10^{-8}$
Phosphorus	0.244
Platelets	0.119
Potassium	0.608

RBC Count	0.004
SGOT (AST)	0.626
SGPT (ALT)	0.084
Sodium	0.114
Thyroxine (T4)	0.571
Total Bilirubin	0.579
Total Cholesterol	0.075
Total Protein	0.020
Uric Acid	0.145
Urine pH (Quan)	0.667
WBC Count	0.876

The overall main effect of rotigotine on hemoglobin during treatment, without considering a trend over time, was an average reduction of 1.55 g/L (95% confidence interval (CI), 1.00 – 2.10, $p<10^{-7}$), or about 1%. There was strong evidence of a linear trend, with a decline for rotigotine subjects relative to placebo subjects of 0.10 g/L per week (95% CI 0.07-0.14, $p<10^{-9}$) with no evidence for attenuation over time (p=0.99 for a quadratic term). Observations of linear trends are listed in Reviewer's Table 7.1.7.4.2. Similar trends were seen separately in all three of the S1 Pool studies but was of borderline statistical significance in the SP512 study and not significant in SP506. The SP506 study did, however, show borderline significance for a linear dose-response effect. This may be more of a threshold or plateau effect with a negligible effect observed at the lowest (4.5 mg) dosage and greater but similar effects seen at higher dosages. Ropinirole, the active control in the SP513 study, was also associated with a decline in blood hemoglobin levels relative to placebo to a lesser extent and lesser statistical significance than was seen with rotigotine.

Reviewer's Table 7.1.7.4.2:
Estimated Average Rate of Decline in Blood Hemoglobin from Baseline Relative to Placebo

	Rate of decline vs. placebo in g/L per week			
	Estimate	95% CI		p value
All Studies	0.10	0.14	0.07	$<10^{-9}$
SP512	0.05	0.14	(0.03)	0.086
SP513	0.11	0.17	0.05	0.0008
SP506	0.04	0.16	(0.08)	0.51
SP506 D/R				0.061
SP506 excluding 4.5 mg	0.07	0.18	(0.05)	0.283
Pool S1 (All Studies DB part only)	0.08	0.12	0.04	0.00001
Ropinirole (SP513)	0.09	0.15	0.02	0.01

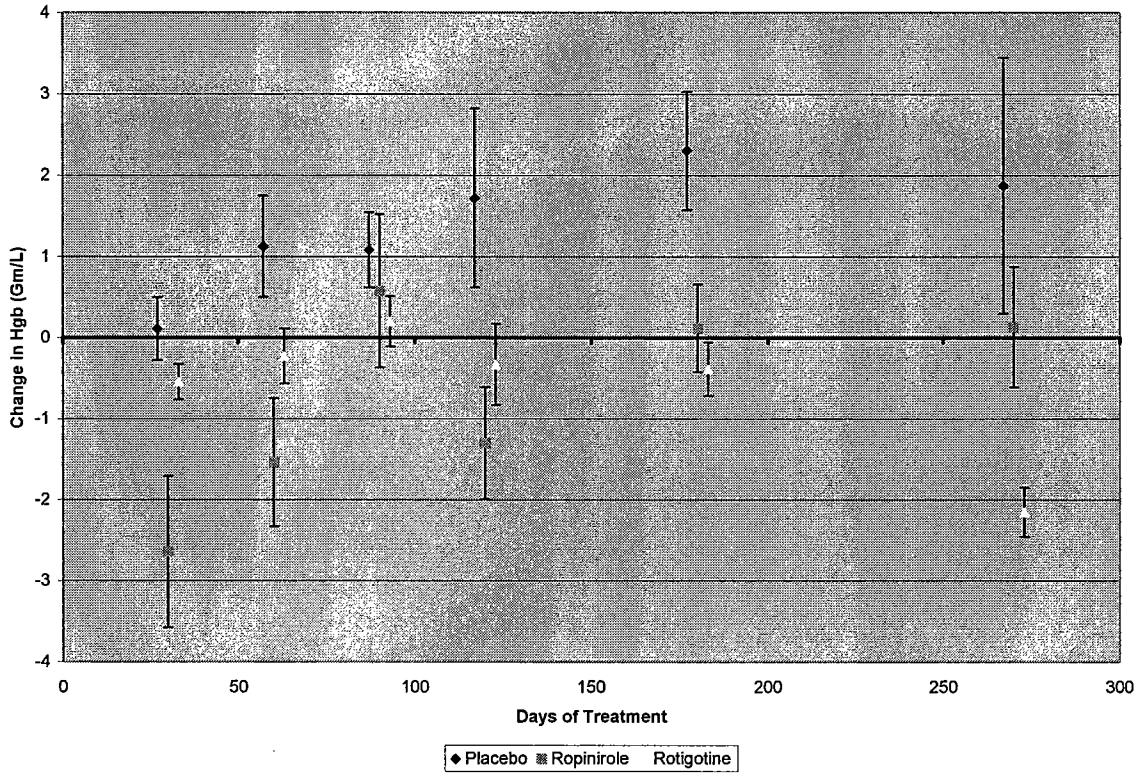
() indicate a negative number
D/R: dose response

Differences in changes in blood hemoglobin levels during specific time periods are shown graphically in Reviewer's Figure 7.1.7.4.1. The points in the graph are the simple averages (with 95% CI) for the observations. The exact numbers are given in Reviewer's Table 7.1.7.4.3. There is

an apparent and unexplained rise in blood hemoglobin levels in the placebo group over baseline that is paralleled at a lower level by the rotigotine group for the first ninety days. In the case of ropinirole, the differences appear greater in the beginning and narrower over time. Looking at the SP513 study alone (Reviewer's Figure 7.1.7.4.2), the differences between placebo and ropinirole fluctuate and are less consistent than the differences between placebo and rotigotine.

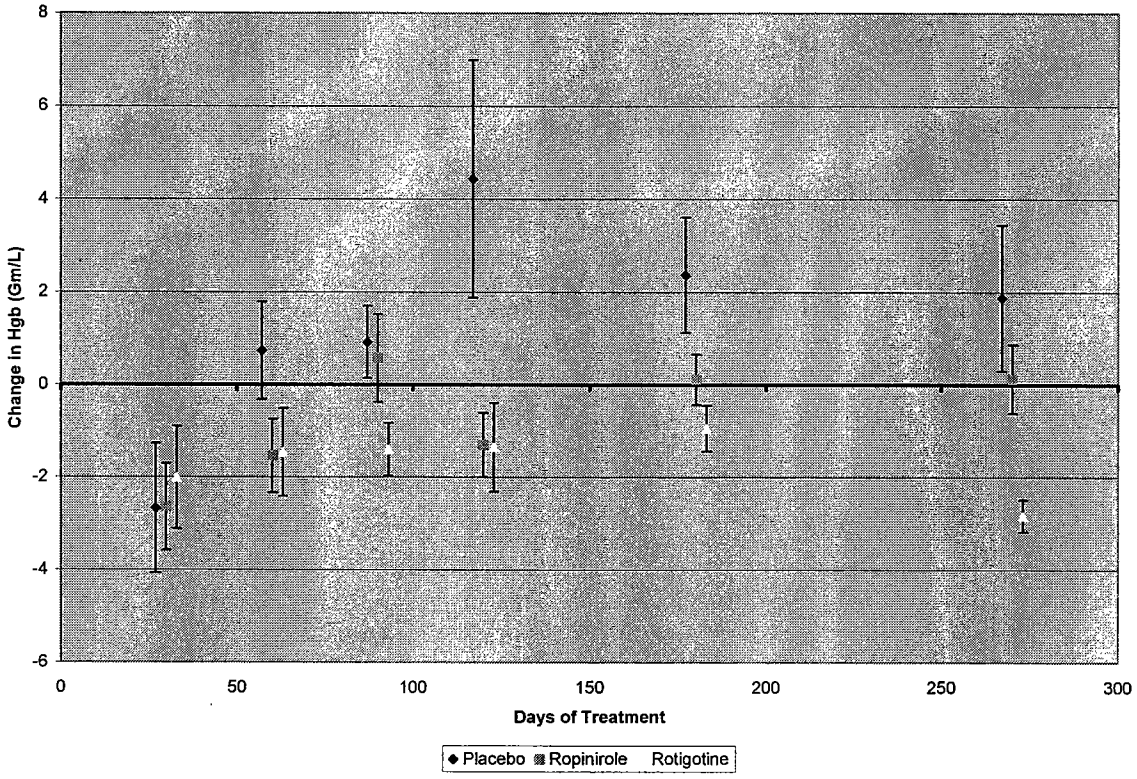
The decline in hemoglobin levels over time appeared to continue during the open label extensions (Pool S6) whether or not subjects initially received rotigotine or placebo. The estimated rate of decline during the open label extensions was 0.019 g/L per week (95% CI 0.007-0.031, p=0.002). For subjects who initially received placebo, the rate of decline was 0.020 g/L per week (95% CI 0.002-0.038, p=0.026) and for subjects who received rotigotine in the double-blind period it was nearly identical, 0.018 g/L per week (95% CI 0.002-0.033, p=0.024). This rate was lower than that observed in the double-blind period but cannot account for continuation of whatever process was leading to elevation of hemoglobin levels in placebo subjects.

Reviewer's Figure 7.1.7.4.1: Average Change from Baseline in Hemoglobin by Time Period and Treatment Assignment for Pool S1 and Subjects originally assigned to Rotigotine in Pool S6



Reviewer's Table 7.1.7.4.3: Average Change from Baseline in Hemoglobin by Time Period and Treatment Assignment for Pool S1 and Subjects originally assigned to Rotigotine in Pool S6						
Time Period	Placebo			Rotigotine		
	Change	95%CI		Change	95%CI	
Days 1-44	0.02	0.79	(0.74)	(0.52)	(0.09)	(0.94)
Days 45-74	1.09	2.30	(0.12)	(0.22)	0.45	(0.89)
Days 75-104	1.06	1.97	0.15	0.21	0.81	(0.40)
Days 105-149	1.72	3.87	(0.43)	(0.33)	0.65	(1.31)
Days 150-224	2.30	3.72	0.88	(0.39)	0.26	(1.03)
Days 225 and Later	1.87	4.96	(1.22)	(2.15)	(1.56)	(2.75)

Reviewer's Figure 7.1.7.4.2: Average Change from Baseline in Hemoglobin by Time Period and Treatment Assignment in Study SP513



The negative effect of rotigotine on hemoglobin levels is confirmed by threshold analyses. These were calculated using a random effects logit model by looking at whether subject had a value exceeding the threshold each time the test was performed. These results are given in Reviewer's Table 7.1.7.4.4.

Reviewer's Table 7.1.7.4.4: Relative Risk of Crossing Threshold Values for Rotigotine vs. Placebo				
Study	Estimate	95% CI		p value
	Risk of a below normal Hgb value			
All Studies	2.97	1.72	5.12	0.00005
SP512	2.57	1.08	6.15	0.03
SP513	2.91	1.32	6.42	0.01
SP506	4.39	1.03	18.61	0.05
SP506 D/R				0.12
SP506 D/R Quadratic (plateau effect)				0.09
	Risk of above normal Hgb value			
All Studies	0.62	0.26	1.48	0.29
SP512	0.38	0.07	2.14	0.27
SP513	0.34	0.10	1.14	0.08
SP506	NA[a]			
	Risk of 20 g/L drop from baseline in Hgb			
All Studies	4.07	1.18	14.11	0.027
SP512	4.83	0.58	40.18	0.145
SP513	3.24	0.68	15.54	0.142
SP506	NA[a]			
	Risk of 10 g/L drop from baseline in Hgb			
All Studies	3.32	1.98	5.55	0.00001
SP512	4.22	1.56	11.43	0.005
SP513	5.14	2.26	11.71	0.0001
SP506	1.19	0.52	2.71	0.679
[a] Not calculable due to absence of events in either rotigotine or placebo groups				

In order to get a better sense of how rotigotine affects hemoglobin levels, changes in hemoglobin levels were compared to changes in mean cellular volume (MCV, calculated as hematocrit/RBC count). The mixed effects model was used to examine the within-subject relationship between changes in hemoglobin levels and changes in MCV. The results are shown in Reviewer's Table 7.1.7.4.5. There was no relationship seen in placebo subjects in the double blind period and, at best, a slight suggestion among rotigotine subjects; this may be due to the upward drift in hemoglobin levels during the double-blind period. During the open-label period, changes in hemoglobin levels show a strong positive correlation with changes in MCV, particularly among subjects who had been on rotigotine during the double-blind phase as well. Because the decline in hemoglobin levels associated with rotigotine appears to be accompanied by a decline in MCV, the process causing the decline is likely to be microcytic, involving a loss of iron or a general suppression of erythropoiesis.

Reviewer's Table 7.1.7.4.5: Change in MCV* for 10 g/L Change in Hemoglobin					
	Estimate	95% CI		P value	Correlation Coefficient (r)
Rotigotine Double Blind	0.09	(0.07)	0.24	0.27	0.22
Open Label Placebo	0.26	(0.03)	0.56	0.08	0.14
Open Label Rotigotine	1.25	1.04	1.45	$<10^{-9}$	0.36
All Open Label	0.98	0.81	1.15	$<10^{-9}$	0.30
All rotigotine	0.70	0.58	0.81	$<10^{-9}$	0.21
Placebo Double Blind	0.01	(0.15)	0.16	0.94	0.13

*The normal range for MCV is 78 – 102 fl.

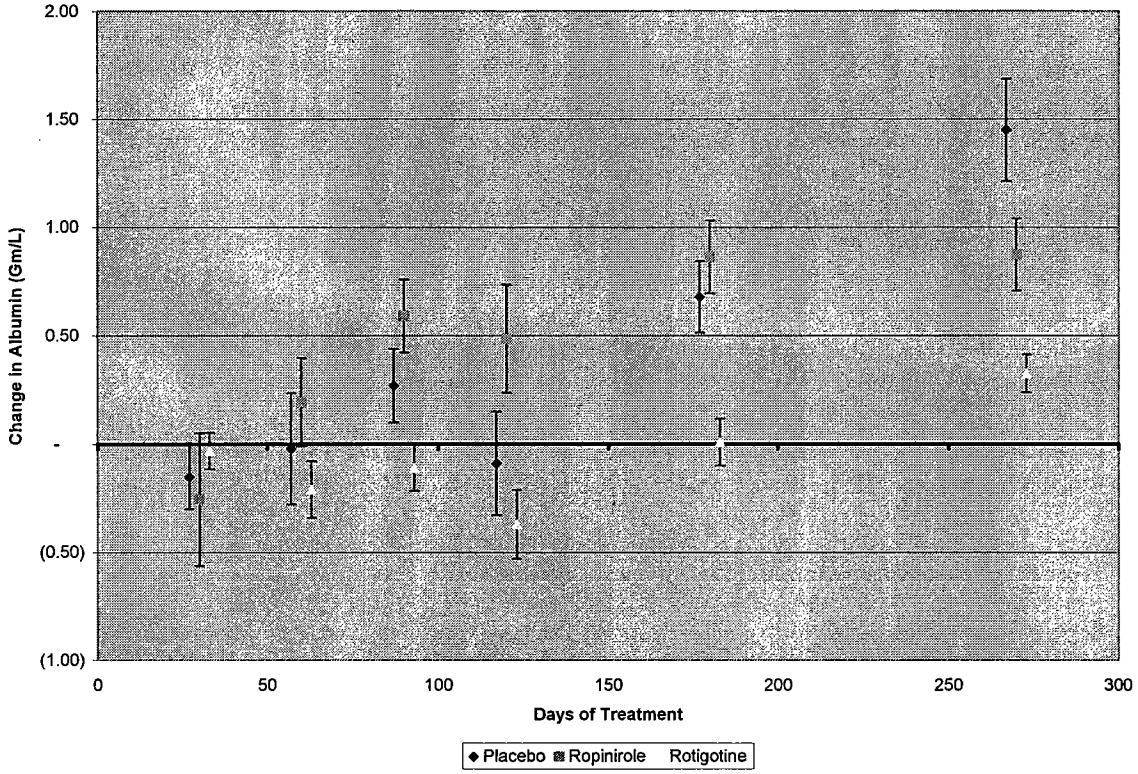
The changes observed in serum albumin levels were similar to those seen with blood hemoglobin. Once again the sponsor's data is reported in SI units, g/L, rather than the conventional g/dL, giving results that are nominally ten times greater in magnitude. The overall main effect of rotigotine on albumin during treatment, without considering a trend over time, was a reduction of 0.194 g/L (95% CI, -0.086 – 0.474, p=0.175) relative to placebo, not statistically significant probably because of a lag in time needed to observe a difference. Beyond 29 days of treatment, the observed main effect was a reduction of 0.307 g/L (95% CI 0.008 – 0.606, p=0.044) and after 59 days 0.339 g/L (95% CI 0.029 – 0.649, p=0.032), again about 1%. There was, again, strong evidence of a linear trend, with a decline for rotigotine subjects relative to placebo subjects of 0.020 g/L per week (95% CI 0.007-0.032, p=0.003). Observations of linear trends are listed in Reviewer's Table 7.1.7.4.6. Similar trends were seen separately in all three of the S1 Pool studies but was of borderline statistical significance in the SP513 and SP506 studies and not significant in SP512. The SP506 study did show a significant linear dose-response effect; in this case there was no suggestion of a threshold or plateau effect. There was no indication of an effect on serum albumin from ropinirole in the SP513 study.

Reviewer's Table 7.1.7.4.6: Estimated Average Rate of Decline in Serum Albumin from Baseline Relative to Placebo				
	Rate of decline vs. placebo in g/L per week			
	Estimate	95% CI		p value
All Studies	0.020	0.032	0.007	0.003
SP512	0.012	0.032	(0.007)	0.214
SP513	0.019	0.038	(0.001)	0.058
SP506	0.053	0.107	(0.002)	0.057
SP506 D/R				0.035
Pool S1 (All Studies DB part only)	0.019	0.033	0.004	0.012
Ropinirole (SP513)	0.004	0.019	(0.012)	0.654

Differences in changes in serum albumin levels during specific time periods are shown graphically in Reviewer's Figure 7.1.7.4.3. The difference appears to be due to rising serum albumin levels in

placebo (and ropinirole). Using the mixed effects model, serum albumin levels rose an average of 0.024 g/L per week (95% CI 0.012 – 0.035, p=0.00004) in placebo subjects but also rose (at a lower rate) an average of 0.004 g/L per week (95% CI 0.001 – 0.006, p=0.005) in rotigotine subjects. The most plausible explanation for the observation of rising albumin levels is that changes in collection or laboratory techniques may have obscured a fall in albumin levels in rotigotine subjects. Because this trend in measured albumin levels does not appear to abate with time, it is impossible to determine what effect rotigotine may have had on subjects switching from placebo in the open-label phases of SP512 and SP513.

Reviewer's Figure 7.1.7.4.3:
Average Change from Baseline in Albumin by Time Period and Treatment Assignment



This secular (and, presumably, artifactual) trend of increasing albumin levels makes it difficult to find a difference between rotigotine and placebo recipients in the incidence of large shifts in serum albumin below thresholds. As shown in Reviewer's Table 7.1.7.4.7, declines of any magnitude appear to have been more common among rotigotine subjects but the differences become less clear as the thresholds become larger.

Reviewer's Table 7.1.7.4.7: Relative Risk of Crossing Threshold Values for Rotigotine vs. Placebo				
Change in Serum Albumin	Estimate	95% CI		p value
Any Decline	1.78	1.25	2.53	0.001
More than 1 g/L	1.88	1.27	2.77	0.002
More than 2 g/L	1.60	1.03	2.50	0.036
More than 3 g/L	1.45	0.86	2.45	0.165
More than 4 g/L	1.33	0.72	2.45	0.360

Changes in albumin appear to be closely related to changes in hemoglobin in rotigotine subjects but less so in placebo subjects. Reviewer's Table 7.1.7.4.8 indicates that a 1 g/L decline in blood hemoglobin in rotigotine was accompanied by a decline of an average of 0.2 g/L in serum albumin.

Reviewer's Table 7.1.7.4.8: Change in Albumin (in g/L) for 1 g/L change in Hemoglobin					
	Estimate	95% CI		p value	Correlation Coefficient (r)
All Rotigotine	0.192	0.149	0.235	$<10^{-9}$	0.555
Rotigotine Double Blind	0.195	0.155	0.235	$<10^{-9}$	0.562
All Open Label	0.150	0.095	0.205	$<10^{-7}$	0.433
Placebo Double Blind	0.079	(0.026)	0.185	0.141	0.430

As noted in above, rotigotine was associated with a steady decline in hemoglobin and albumin levels over time relative to placebo in the S1 pool. The decline in hemoglobin amounted to an average about 0.25 g/dl or 2% at the end of a 6 month study period. Because this decline was steady and without evidence of attenuation, it can, reasonably be extrapolated to 0.5 g/dl or 4% over one year of treatment. The rate of decline in albumin corresponded to about 2.5% per year of treatment; the observed difference at six months was about 0.08 g/dl or 2%. These are averages; a substantial proportion of patients can be expected to see declines that are considerably larger while many would be unaffected. It was also noted that these changes were not independent; they tended to occur in the same subjects in conjunction with a decline in mean corpuscular volume. Although there were no statistically significant differences between rotigotine and placebo groups in most other laboratory tests, it is possible that subjects who experienced declines in hemoglobin and albumin associated with rotigotine may have had specific changes in other laboratory parameters that were not detectable at the level of group differences. Reviewer's Table 7.1.7.4.9 shows the correlations between changes in blood hemoglobin and other laboratory tests for rotigotine and placebo subjects. The table also includes beta coefficients, representing the percent change in each laboratory parameter corresponding to a one percent increase in hemoglobin, as well as p values.

Most of the changes in other laboratory values showed a significant positive correlation with hemoglobin that was usually stronger in rotigotine subjects. For some of these tests, such as liver

enzymes, a decline would be considered benign and could be the result of increased clearance, dilution due to fluid retention or changes in laboratory or collection technique. Dilution would seem an unlikely explanation given the absence of any relationship between changes in blood hemoglobin and changes in serum sodium and only a very slight inverse correlation between blood hemoglobin and weight: a 10% decline in blood hemoglobin would correspond to only a 0.1% increase in weight.

The most interesting findings may be the inverse correlations between changes in hemoglobin and serum chloride, urine pH and blood urea nitrogen (BUN). These relationships were stronger in rotigotine subjects; hemoglobin was *positively* correlated with BUN among placebo subjects. Looking at these correlations from a clinical perspective, declining hemoglobin levels among rotigotine subjects appeared to correspond to decreasing renal perfusion (rising BUN with no change in serum creatinine) and increasing metabolic acidosis of renal origin (increasing serum chloride and urine pH).

Reviewer's Table 7.1.7.4.9: Correlation of Changes in Hemoglobin Levels with Changes Other Laboratory Values (and Subject Weight)

	Placebo	Rotigotine	Placebo	Rotigotine	Placebo	Rotigotine
	r	r	beta	beta	p	p
HEMATOCRIT	0.629	0.884	0.40	0.92	0.0385	0.0000
TOTAL BILIRUBIN	0.091	0.219	0.51	1.17	0.0193	0.0000
TOTAL CHOLESTEROL	0.270	0.395	0.31	0.79	0.1585	0.0000
RBC COUNT	0.647	0.846	0.39	0.80	0.0500	0.0000
GGT	0.010	0.100	0.02	0.83	0.9124	0.0000
CALCIUM	0.236	0.374	0.15	0.26	0.0524	0.0000
SGPT (ALT)	0.063	0.142	0.32	1.00	0.0000	0.0000
CHLORIDE	(0.152)	(0.202)	(0.06)	(0.09)	0.0114	0.0000
POTASSIUM	0.144	0.095	0.17	0.15	0.0414	0.0000
THYROXINE (T4)	NA	NA	0.61	0.55	0.0001	0.0000
URINE PH (QUAN)	(0.014)	(0.093)	(0.07)	(0.13)	0.3628	0.0000
EOSINOPHILS	(0.037)	(0.069)	(0.22)	(0.76)	0.4839	0.0000
GLOBULIN	0.275	0.334	0.07	0.11	0.0500	0.0000
TOTAL PROTEIN	0.433	0.511	0.29	0.50	0.0969	0.0000
SGOT (AST)	0.047	0.138	0.14	0.58	0.1310	0.0000
ALBUMIN	0.390	0.464	0.26	0.47	0.1389	0.0000
LYMPHOCYTES ABSOLUTE	0.148	0.120	0.23	0.47	0.0053	0.0000
ALKALINE PHOSPHATASE	0.094	0.132	0.08	0.46	0.6818	0.0003
URIC ACID	0.030	0.064	0.13	0.25	0.1527	0.0005
BUN	0.010	(0.062)	0.13	(0.18)	0.0000	0.0021
GLUCOSE	(0.070)	0.000	(0.24)	(0.20)	0.0232	0.0029
INORGANIC PHOSPHATE	0.110	0.042	0.35	0.17	0.0000	0.0029
MONOCYTES	(0.033)	0.000	(0.13)	0.05	0.1615	0.0332
WEIGHT	(0.020)	(0.026)	(0.05)	(0.01)	0.1300	0.0340
BASOPHILS ABSOLUTE	(0.030)	0.026	(1.18)	0.47	0.4295	0.0601
PLATELET COUNT	0.094	(0.051)	0.19	(0.31)	0.0536	0.1141
EOSINOPHILS ABSOLUTE	0.000	(0.036)	0.07	(0.43)	0.8729	0.1362

WBC COUNT	0.122	0.121	0.25	0.33	0.0091	0.1936
BASOPHILS	(0.039)	0.000	(1.12)	0.19	0.2380	0.2301
MONOCYTES ABSOLUTE	0.022	0.045	0.05	0.28	0.6241	0.3524
CREATININE	0.099	0.063	0.19	0.18	0.0001	0.3735
NEUTROPHILS ABSOLUTE	0.066	0.088	0.23	0.26	0.0536	0.3789
LYMPHOCYTES	0.037	0.000	0.01	0.10	0.9283	0.4473
BICARBONATE	NA	NA	0.11	0.07	0.5892	0.5157
NEUTROPHILS	0.010	(0.014)	0.02	(0.02)	0.7188	0.6599
SODIUM	(0.010)	0.000	(0.00)	(0.00)	0.7949	0.8808

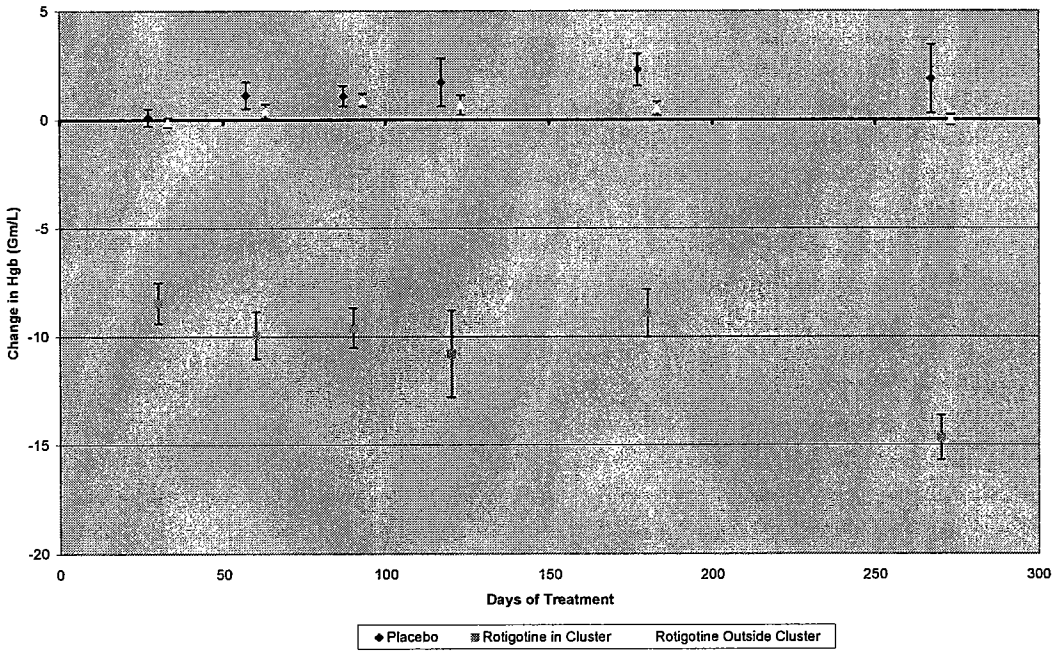
Note: Ranked by decreasing statistical significance in the rotigotine group.

Cluster analysis was performed to identify subjects with this clinical picture. Using the mean change from baseline of all values obtained while on treatment, the analysis divided all subjects into six different groups according to similarities in changes in hemoglobin, chloride, BUN and albumin. One cluster of 64 subjects showed a pattern of decreases in hemoglobin albumin and total cholesterol and increases in chloride, BUN and urine pH (Reviewer's Table 7.1.7.4.10). The significantly larger decline in total cholesterol levels in the cluster that accompanied the declines in hemoglobin and albumin, even though cholesterol levels were not used in cluster selection, supports a clinical picture of inflammation. There were 54 rotigotine-treated subjects (9% of all rotigotine subjects) and 10 placebo subjects (4%) in the cluster, a significant difference (Odds ratio 2.46, 95% confidence interval, 1.23-4.89, p=0.011). As shown in Reviewer's Figure 7.1.7.4.4, almost all of the difference in change in hemoglobin between the rotigotine and placebo groups occurred in the rotigotine subjects in the cluster.

Reviewer's Table7.1.7.4.10: Changes in Laboratory Values for Subjects included and not included in Cluster

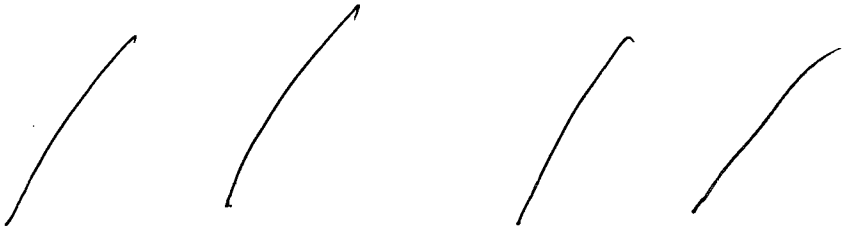
	Included in Cluster			Not included in Cluster				
	Number	Mean Change	SEM	Number	Mean Change	SEM	Percent difference	p value
Hemoglobin (Gm/L)	64	(11.78)	0.51	830	0.79	0.20	10%	0.000
Chloride (mg/dl)	64	0.66	0.30	844	(0.31)	0.07	1%	0.003
BUN (mg/dl)	64	0.56	0.15	844	0.11	0.04	4%	0.005
Albumin (Gm/L)	64	(1.48)	0.22	844	0.24	0.07	5%	0.000
Total Cholesterol (mmol/L)	54	(0.45)	(0.06)	540	(0.11)	0.02	8%	0.000
Urine pH	54	0.10	0.09	545	(0.03)	0.03	2%	0.180

Reviewer's Figure 7.1.7.4.4:
Average Change from Baseline in Hemoglobin by Time Period, Cluster Assignment for Rotigotine Subjects and Treatment Assignment



Reviewer's Conclusions and Recommendations Regarding Laboratory Test Results
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; this resemblance suggests that the explanation for these observations may not be benign. Although no subjects suffered serious consequences from anemia or hypoalbuminemia during clinical trials, there are no data that would indicate whether 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 without the close monitoring available in clinical trials, 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 abnormal or markedly low platelet and leukocyte, particularly monocyte, counts suggest an effect on hematopoiesis that goes beyond erythrocytes.

It is not possible to write an adequate label for this drug until this process of declining hemoglobin and albumin levels is better characterized. In order to better understand the effect of rotigotine on blood hemoglobin and serum albumin levels, the following information is needed:

5. Complete clinical documentation of subjects with markedly abnormal laboratory values listed in Appendix 2 prior to approval.
6. Also — . there must be 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. These studies need to include continued detailed monitoring during post-treatment washout in order to assess rate of recovery from reduction of hemoglobin and albumin.
7. 

Vital Signs

7.1.7.5 Overview of vital signs testing in the development program

The principal randomized controlled double-blind studies considered in this application are the SP506, SP512, and SP513 studies, combined by the sponsor into the S1 Pool. In SP512 and SP513, heart rate and blood pressure were measured at each assessment after 2 minutes of rest. While supine, the blood pressure and heart rate were measured after 1 minute and then again after 5 minutes. Subjects then had blood pressure and heart rate measured 1 minute and 3 minutes after standing. The lowest supine value of the systolic blood pressure value was used to determine whether the subject had orthostatic hypotension. A drop in systolic blood pressure of ≥20mmHg and/or a drop of ≥10mmHg in diastolic blood pressure on standing were considered indicative of orthostatic hypotension. Subject weight, wearing light clothing, was also recorded at each visit. In SP506, resting heart rate and blood pressure were assessed at each visit. To assess orthostatic hypotension, blood pressure, and heart rate, measurements were taken 3 minutes after the subject stood up from their reclined initial position. Orthostatic hypotension was defined as a drop in systolic blood pressure of 30mmHg or greater upon standing.

The application also contains vital sign data from the SP534, SP535 and SP540 studies of rotigotine in early Parkinson's disease and the SP533, SP591 and SP511 studies of advanced-stage Parkinson's. In SP534 Part 1, heart rate, blood pressure, oral temperature, and respiratory rate were assessed at each clinic visit. Weight was measured at screening, the end of the dose-maintenance period, and at any premature withdrawal visit. In SP534 Part 2, heart rate, sitting blood pressure, temperature, and respiratory rate were assessed at each clinic visit. Weight was assessed at screening, end of titration, safety follow-up, and premature withdrawal. At each dose-escalation step, both sitting and standing blood pressure were measured after patch application (6 and 12 hours post) to assess orthostatic hypotension. In SP535, heart rate, blood pressure, oral temperature, and respiratory rate were assessed at each visit after the subject had been at rest for 2 minutes. Systolic

and diastolic blood pressure and heart rate were measured while sitting and while standing at the start of the placebo run-in period and while sitting only during the rest of the trial. Weight was measured at screening, safety follow-up, and at any premature withdrawal visit. In SP540, heart rate, blood pressure, oral temperature, and respiratory rate were assessed at each visit. Blood pressure and heart rate were measured 3 times at 2-minute intervals. After the last measurement, the subject was asked to stand up and the blood pressure and heart rate were measured at 1-minute intervals for 5 minutes. Weight was also collected during the trial. In SP511 and SP591, heart rate, blood pressure, temperature, and respiratory rate were assessed at every clinic visit. Orthostatic hypotension and weight were assessed at screening only. In SP533, heart rate and sitting blood pressure were measured immediately prior to patch removal (prior to patch application on Day 1) and every hour during waking hours on all inpatient days. Weight was measured at screening, at the end of dose maintenance (Day 29), at safety follow-up, and at any premature withdrawal visit.

7.1.7.6 Selection of studies and analyses for overall drug-control comparisons

All of the Phase 2 and Phase 3 studies containing vital sign data can be analyzed as changes compared to baseline. The placebo-controlled studies (SP506, SP512, SP513, SP534 Parts 1 and 2, SP535 and SP 511) can compare time-matched changes from baseline between active-drug and placebo-treated groups. To make roughly comparable assessments across studies, measurements are classified as baseline, titration or dose escalation phase, maintenance phase, or follow-up (off drug).

In the Summary of Clinical Safety, the Sponsor uses the combined results of the three principal studies as the primary analysis of vital signs, reporting change from baseline for the 5 minute supine readings obtained at the end of treatment

7.1.7.7 Standard analyses and explorations of vital signs data

7.1.7.7.1 Analyses focused on measures of central tendencies

Mean changes from baseline reported by the Sponsor are shown in Reviewer's Tables 7.1.8.3.1.1 and 7.1.8.3.1.2 for the S1 Pool. These measurements are described as "end of treatment" which is ambiguous; it is not clear whether subjects who withdrew from the study had these measurements taken while they were still taking the randomized treatment.

Reviewer's Table 7.1.8.3.1.1: Mean change from baseline at end of treatment (supine 5 minute)

Vital sign	Placebo n=287 Mean±SD	Rotigotine n=648 Mean±SD
Heart rate (bpm)	1.5±9.98	0.4±9.88
Systolic blood pressure (mmHg)	-0.8±14.86	-1.6±14.59
Diastolic blood pressure (mmHg)	-0.1±9.05	-1.4±8.95
Weight	-0.3±2.99	-0.1±3.22

Sponsor's Data source: ISS Table 98.1, ISS Table 99.1, ISS Table 100.1

Reviewer's Table 7.1.8.3.1.2: Mean change from baseline at end of treatment: Change from standing 1 minute – supine 5 minute

Vital sign	Placebo n=211 Mean±SD	Rotigotine n=395 Mean±SD
Heart rate	-0.2±7.63	-0.1±7.51
Systolic blood pressure	-1.2±12.01	-0.5±12.73
Diastolic blood pressure	-0.7±7.80	-0.1±8.10

Sponsor's Data source: ISS Table 98.1, ISS Table 99.1, ISS Table 100.1

7.1.7.7.2 Analyses focused on outliers or shifts from normal to abnormal

The proportions of subjects who recorded a change in heart rate at any time from baseline of more than either 15 or 30 beats per minute (bpm) are shown in Reviewer's Table 7.1.8.3.2.1 for the pooled samples from Pool S1. There was a higher incidence of 15 bpm increases, both standing and supine, among subjects receiving higher doses and a lower incidence of 15 bpm decreases, both standing and supine, among all dose levels in subjects treated with rotigotine compared to placebo. Rotigotine did not appear to affect orthostatic changes in heart rate.

The proportions of subjects in the pooled samples who recorded a change in systolic blood pressure at any time from baseline of more than either 20 or 40 mmHg are shown in Reviewer's Table 7.1.8.3.2.2 and for a change in diastolic blood pressure of more than either 10 or 20 mmHg in Reviewer's Table 7.1.8.3.2.3. There is an appearance of a dose-response relationship showing increasing incidence of both increases and decreases of both systolic and diastolic blood pressure across all thresholds, whether supine or standing. However, these incidences exceeded the rates observed with placebo only at higher doses, suggesting that lower doses are associated with greater stability in blood pressure than was seen with placebo subjects. There then appears to be a second effect where the stability wanes as dose increases. Because most subjects were treated under flexible dosing protocols, it cannot be determined whether these observations are a reflection of drug effect or differences in subject characteristics.

Reviewer's Table 7.1.8.3.2.4 shows the incidence of changes in weight of more than ten percent from baseline. These changes occurred more frequently in rotigotine treated subjects, particularly at higher dosages.

Reviewer's Table 7.1.8.3.2.1:
Large Shifts from Baseline in Heart Rate at Any Visit, by Modal Dose

Dose	Placebo		4.5 mg		9 mg		13.5 mg		18 mg		All Rotigotine	
No. of Subjects	289	%	104	%	68	%	223	%	254	%	649	%
Supine												
Increment >= 15 bpm	85	29%	23	22%	16	24%	82	37%	90	35%	211	33%
Increment >= 30 bpm	14	5%	1	1%	2	3%	8	4%	8	3%	19	3%
Decrement >= 15 bpm	57	20%	14	13%	8	12%	40	18%	47	19%	109	17%
Decrement >= 30 bpm	4	1%	1	1%	0	0%	1	0%	4	2%	6	1%
Standing												
Increment >= 15 bpm	76	26%	20	19%	13	19%	84	38%	85	33%	202	31%
Increment >= 30 bpm	11	4%	0	0%	1	1%	9	4%	8	3%	18	3%
Decrement >= 15 bpm	70	24%	20	19%	12	18%	40	18%	48	19%	120	18%
Decrement >= 30 bpm	3	1%	1	1%	0	0%	3	1%	7	3%	11	2%
Change from Supine to Standing												
Increment >= 15 bpm	46	16%	3	3%	2	3%	51	23%	35	14%	91	14%
Increment >= 30 bpm	3	1%	0	0%	0	0%	8	4%	3	1%	11	2%
Decrement >= 15 bpm	46	16%	6	6%	5	7%	40	18%	31	12%	82	13%
Decrement >= 30 bpm	4	1%	0	0%	0	0%	5	2%	4	2%	9	1%

Note: Subjects are counted once during treatment regardless of the number of times achieving the threshold change.
Note: The listed dosages are those most common received by subjects
Source: Sponsor's ISS Table 120.1

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Reviewer's Table 7.1.8.3.2.2:
Large Shifts from Baseline in Systolic Blood Pressure at Any Visit, by Modal Dose

			Rotigotine (mg/day)									
	Placebo		4.5		9		13.5		18		All rotigotine	
Position/	N=289		N=104		N=68		N=223		N=254		N=649	
Change	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)		
Supine												
Increment >= 20 mmHg	105	36.3%	24	23.1%	20	29.4%	84	37.7%	96	37.8%	224	34.5%
Increment >= 40 mmHg	3	1.0%	4	3.8%	1	1.5%	11	4.9%	15	5.9%	31	4.8%
Decrement >= 20 mmHg	120	41.5%	16	15.4%	16	23.5%	78	35.0%	116	45.7%	226	34.8%
Decrement >= 40 mmHg	11	3.8%	3	2.9%	3	4.4%	11	4.9%	18	7.1%	35	5.4%
Standing												
Increment >= 20 mmHg	96	33.2%	19	18.3%	16	23.5%	67	30.0%	95	37.4%	197	30.4%
Increment >= 40 mmHg	8	2.8%	2	1.9%	1	1.5%	13	5.8%	20	7.9%	36	5.5%
Decrement >= 20 mmHg	120	41.5%	25	24.0%	21	30.9%	88	39.5%	105	41.3%	239	36.8%
Decrement >= 40 mmHg	15	5.2%	5	4.8%	1	1.5%	13	5.8%	21	8.3%	40	6.2%
Change from Supine to Standing												
Increment >= 20 mmHg	65	22.5%	8	7.7%	10	14.7%	64	28.7%	68	26.8%	150	23.1%
Increment >= 40 mmHg	7	2.4%	0	0%	5	2.2%	8	3.1%	0	0%	13	2.0%
Decrement >= 20 mmHg	82	28.4%	20	19.2%	15	22.1%	59	26.5%	67	26.4%	161	24.8%
Decrement >= 40 mmHg	5	1.7%	3	2.9%	2	2.9%	11	4.9%	4	1.6%	20	3.1%

Source: Sponsor's ISS Table 126.1

Reviewer's Table 7.1.8.3.2.3:
Large Shifts from Baseline in Diastolic Blood Pressure at Any Visit, by Modal Dose

			Rotigotine (mg/day)									
	Placebo		4.5		9		13.5		18		All rotigotine	
Position/	N=289		N=104		N=68		N=223		N=254		N=649	
Change	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)		
Supine												
Increment >= 10 mmHg	147	50.9%	36	34.6%	31	45.6%	101	45.3%	146	57.5%	314	48.4%
Increment >= 20 mmHg	44	15.2%	8	7.7%	8	11.8%	23	10.3%	37	14.6%	76	11.7%
Decrement >= 10 mmHg	155	53.6%	41	39.4%	28	41.2%	125	56.1%	160	63.0%	354	54.5%
Decrement >= 20 mmHg	44	15.2%	9	8.7%	3	4.4%	35	15.7%	64	25.2%	111	17.1%
Standing												
Increment >= 10 mmHg	144	49.8%	44	42.3%	28	41.2%	111	49.8%	133	52.4%	316	48.7%
Increment >= 20 mmHg	41	14.2%	10	9.6%	4	5.9%	20	9.0%	46	18.1%	80	12.3%
Decrement >= 10 mmHg	166	57.4%	37	35.6%	32	47.1%	145	65.0%	167	65.7%	381	58.7%
Decrement >= 20 mmHg	54	18.7%	6	5.8%	8	11.8%	42	18.8%	55	21.7%	111	17.1%
Change from Supine to Standing												
Increment >= 10 mmHg	128	44.3%	37	35.6%	21	30.9%	100	44.8%	128	50.4%	286	44.1%
Increment >= 20 mmHg	20	6.9%	10	9.6%	1	1.5%	16	7.2%	39	15.4%	66	10.2%
Decrement >= 10 mmHg	144	49.8%	29	27.9%	29	42.6%	124	55.6%	119	46.9%	301	46.4%
Decrement >= 20 mmHg	32	11.1%	5	4.8%	6	8.8%	27	12.1%	30	11.8%	68	10.5%

Source: Sponsor's ISS Table 132.1

Reviewer's Table 7.1.8.3.2.4:
Change from baseline in weight at any visit during treatment by modal dose

Change criteria	Placebo N=289 n (%)	Rotigotine 4.5mg/day N=104 n (%)	Rotigotine 9.0mg/day N=68 n (%)	Rotigotine 13.5mg/day N=223 n (%)	Rotigotine 18.0mg/day N=254 n (%)	All Rotigotine N=649 n (%)
Increase 10%	0	0	0	11 (5)	5 (2)	16 (2)
Decrease 10%	6 (2)	1 (1)	1 (2)	8 (4)	13 (5)	23 (4)

Sponsor's Data source: ISS Table 97.3

7.1.7.7.3 Marked outliers and dropouts for vital sign abnormalities

There were no reported cases of serious adverse events or discontinuations due to changes or abnormalities in heart rates in any of the Pool S1 or phase 2 studies, and none was reported in studies of advanced-stage Parkinson's or restless legs syndrome. There was one case each of hypertension, hypotension and syncope described as serious adverse events among the 649 subjects receiving rotigotine in Pool S1. There was one additional case of postural hypotension observed among subjects receiving rotigotine during the Phase 2 and Pool S6 studies.

7.1.7.8 Additional analyses and explorations

The information presented by the sponsor provides a limited picture of the observed effect of rotigotine upon vital signs. Average changes from baseline are presented at the end of treatment where "end of treatment" is defined as the last available measurement during that period; it is not completely clear that the subject was still receiving randomized treatment when this measurement occurred. The principal trials were conducted under substantially different protocols; combining them into a single pool can be misleading. The distinctions among dosage levels have considerably different significance in SP506, a fixed dose study, than in studies 512 and 513, which are flexible dose. In order to gain better insight from the available information, this reviewer performed a number of additional analyses.

7.1.7.8.1 Analyses focused on measures of central tendencies

Average change from baseline relative to placebo was calculated for each trial at each observation point during treatment. For the fixed-dose study, averages were calculated for each dosage level as well as for all rotigotine subjects combined. The fixed dose study results for heart rate, systolic and diastolic blood pressure are shown in Reviewer's Tables 7.1.8.4.1.1-7.1.8.4.1.3. The results for the flexible-dose studies are shown graphically in Reviewer's Figures 7.1.8.4.1.1-7.1.8.4.1.3.[6] A qualitative assessment of these results is summarized in Reviewer's Table 7.1.8.4.1.4.

[6] Visit frequency in studies SP512 and SP513 was generally weekly during titration and monthly during maintenance.

Reviewer's Table 7.1.8.4.1.1:
Change in Heart Rate from Baseline Relative to Placebo in SP506 Trial

Visit	Titration	First Maintenance	Second Maintenance	De-Escalation	Follow-up
Supine					
all rotigotine	0.78	0.73	1.37	0.05	(1.12)
4.5 mg	(0.71)	0.38	0.33	(0.93)	(2.48)
9 mg	(0.36)	2.28	0.36	0.32	(0.37)
13.5 mg	1.54	(0.15)	0.29	(0.52)	(1.47)
18 mg	2.49	0.56	4.32	1.37	(0.04)
Standing					
all rotigotine	2.13	1.77	2.25	1.14	0.87
4.5 mg	0.60	2.24	1.95	0.12	0.55
9 mg	1.08	2.94	0.93	1.38	1.28
13.5 mg	2.67	(0.03)	1.48	0.69	0.09
18 mg	4.01	2.00	4.42	2.41	1.59
Change from supine to standing					
all rotigotine	1.34	1.04	0.88	1.15	2.08
4.5 mg	1.30	1.86	1.62	1.26	3.29
9 mg	1.44	0.66	0.57	1.07	1.65
13.5 mg	1.13	0.12	1.19	1.21	1.67
18 mg	1.51	1.44	0.10	1.04	1.63

( ) indicates a negative number

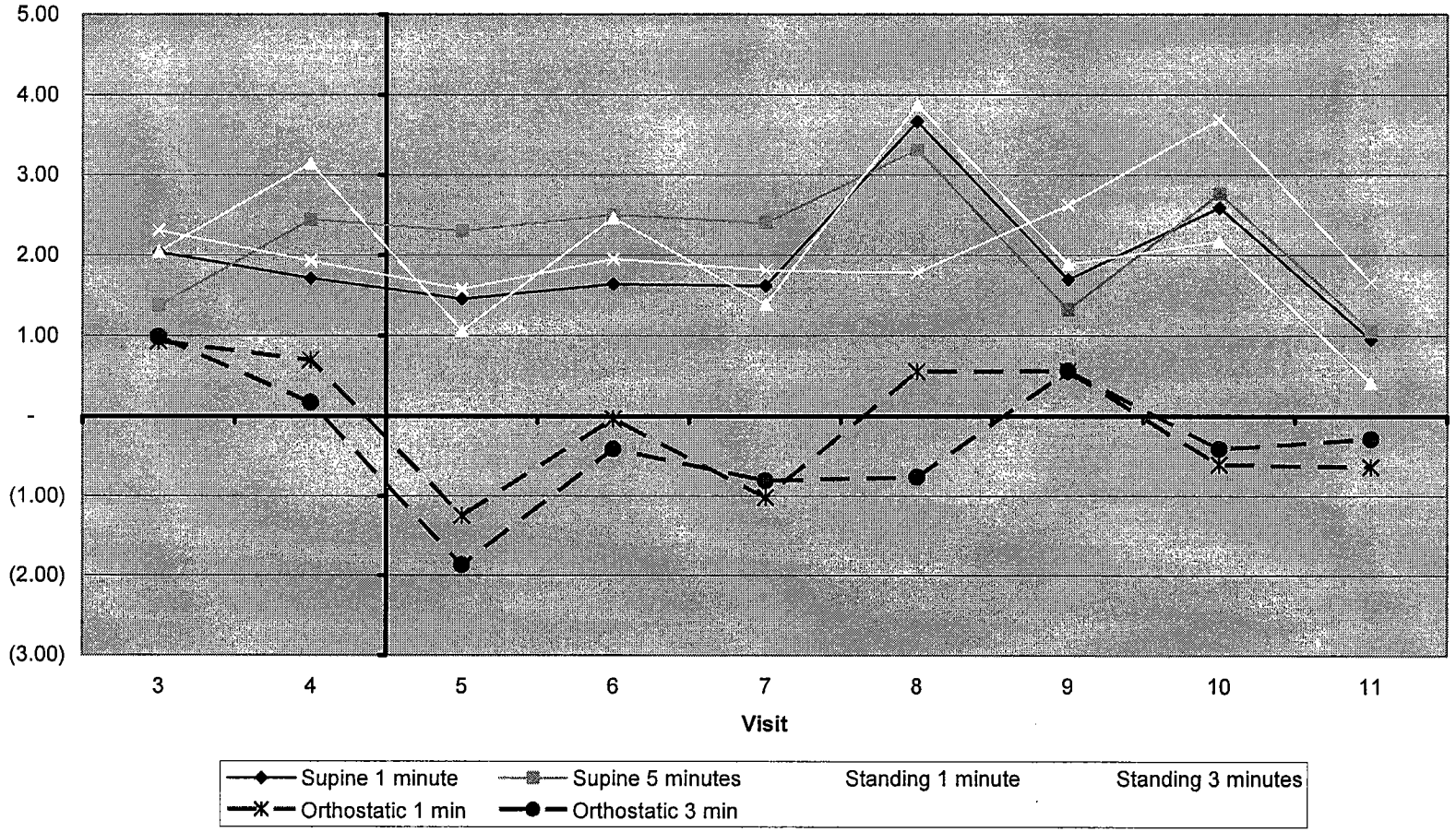
Reviewer's Table 7.1.8.4.1.2:
Change in Systolic Blood Pressure from Baseline Relative to Placebo in SP506 Trial

Visit	Titration	First Maintenance	Second Maintenance	De-Escalation	Follow-up
Supine					
all rotigotine	2.06	2.23	(0.58)	0.96	(0.63)
4.5 mg	1.40	1.05	(2.17)	(1.26)	(1.91)
9 mg	1.92	4.29	1.27	1.57	(0.10)
13.5 mg	5.95	5.32	1.85	3.02	3.13
18 mg	(0.80)	(1.31)	(2.84)	0.76	(3.41)
Standing					
all rotigotine	2.18	(0.57)	(2.50)	0.61	(3.81)
4.5 mg	0.35	(1.46)	(3.85)	(3.69)	(8.18)
9 mg	0.76	1.74	(2.28)	0.61	(3.20)
13.5 mg	5.80	1.30	(2.68)	3.08	(1.02)
18 mg	1.78	(3.46)	(1.15)	2.72	(2.63)
Change from supine to standing					
all rotigotine	0.12	(2.80)	(1.92)	(0.35)	(3.18)
4.5 mg	(1.05)	(2.51)	(1.68)	(2.43)	(6.27)
9 mg	(1.16)	(2.55)	(3.56)	(0.96)	(3.10)
13.5 mg	(0.16)	(4.02)	(4.52)	0.06	(4.15)
18 mg	2.58	(2.15)	1.69	1.96	0.79

Reviewer's Table 7.1.8.4.1.3:
Change in Diastolic Blood Pressure from Baseline Relative to Placebo in SP506 Trial

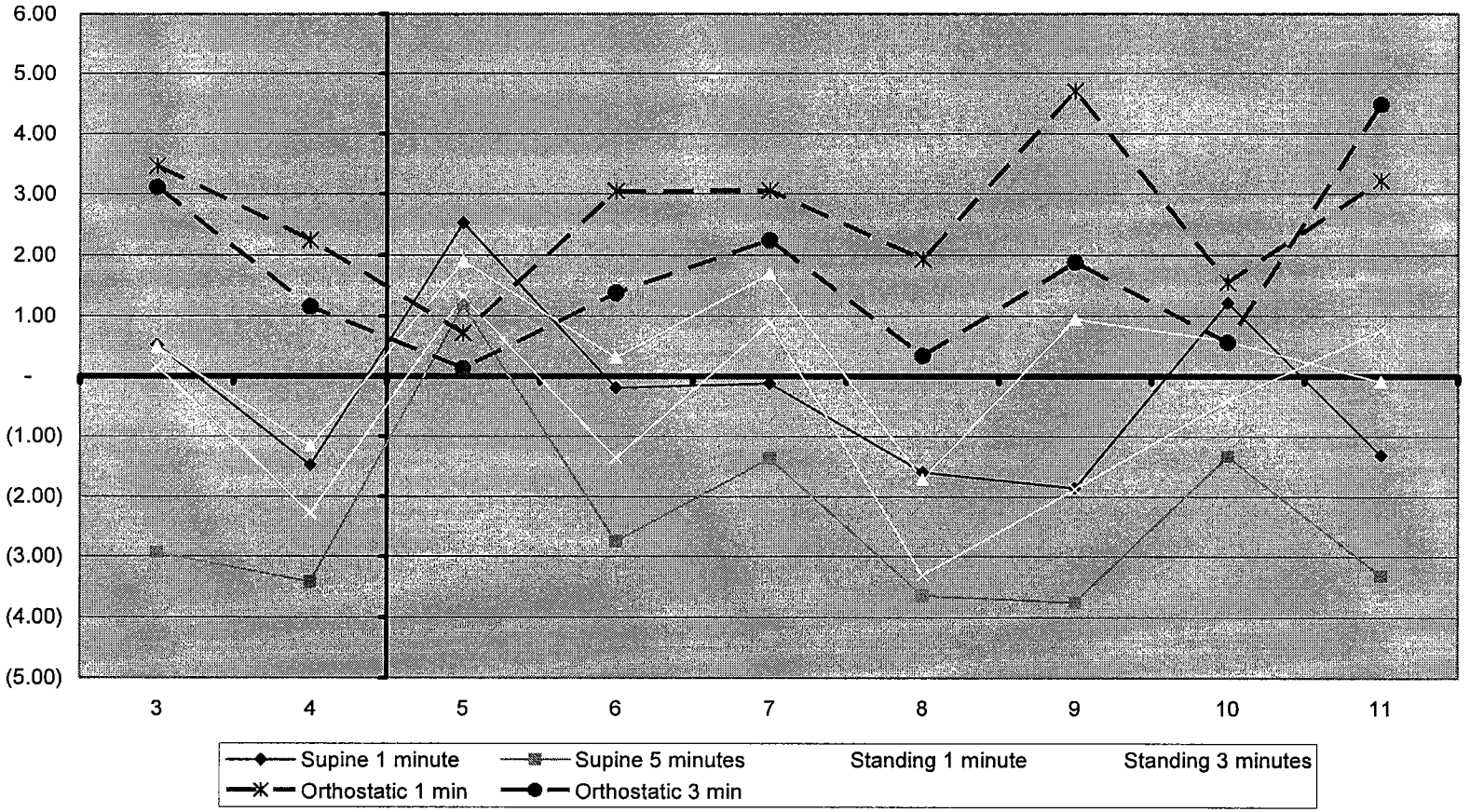
Visit	Titration	First Maintenance	Second Maintenance	De-Escalation	Follow-up
Supine					
all rotigotine	0.69	1.78	0.45	0.99	(0.06)
4.5mg	0.26	1.71	(0.13)	0.53	(1.31)
9mg	(0.07)	2.48	0.95	0.93	0.70
13.5mg	1.00	1.13	0.82	0.37	0.59
18mg	1.45	1.86	0.28	2.11	(0.07)
Standing					
all rotigotine	0.56	0.98	(0.16)	1.87	(0.12)
4.5mg	0.74	2.82	0.10	1.66	(0.11)
9mg	(0.36)	1.01	0.26	1.36	0.10
13.5mg	0.68	(0.02)	(0.05)	2.98	0.89
18mg	1.04	0.10	(0.88)	1.47	(1.28)
Change from supine to standing					
all rotigotine	(0.83)	(0.11)	(0.82)	(0.22)	0.03
4.5mg	(0.22)	1.80	0.02	(0.08)	1.25
9mg	(1.00)	(0.78)	(0.89)	(0.63)	(0.48)
13.5mg	(1.02)	(0.46)	(1.08)	1.56	0.39
18mg	(1.12)	(1.07)	(1.37)	(1.69)	(1.09)

Figure 7.1.8.4.1.1
Change in Heart Rate Relative to Placebo
SP512



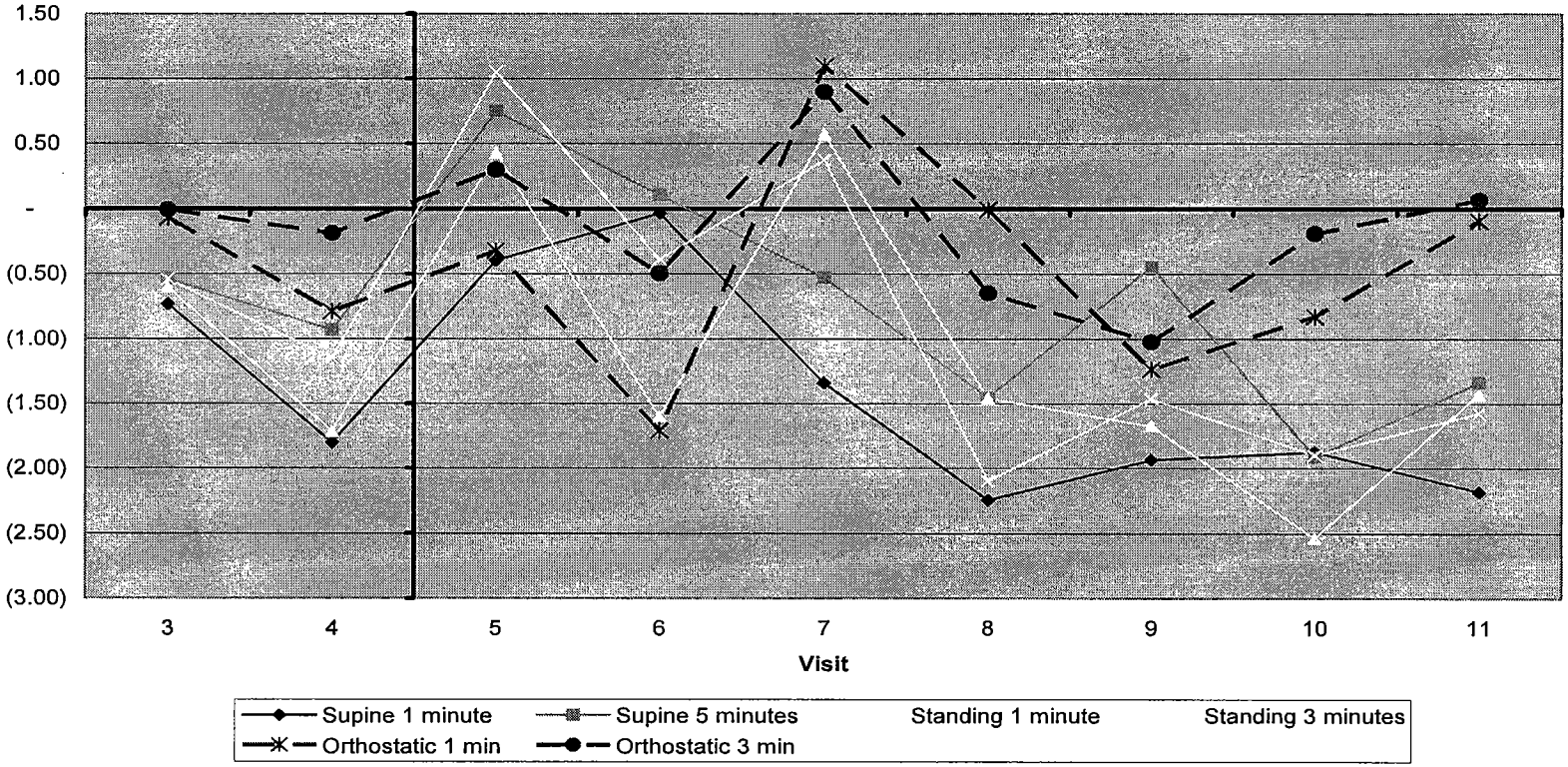
Note: The Y-axis divides the titration period from the maintenance period.

Figure 7.1.8.4.1.2
Change in SBP Relative to Placebo
SP512



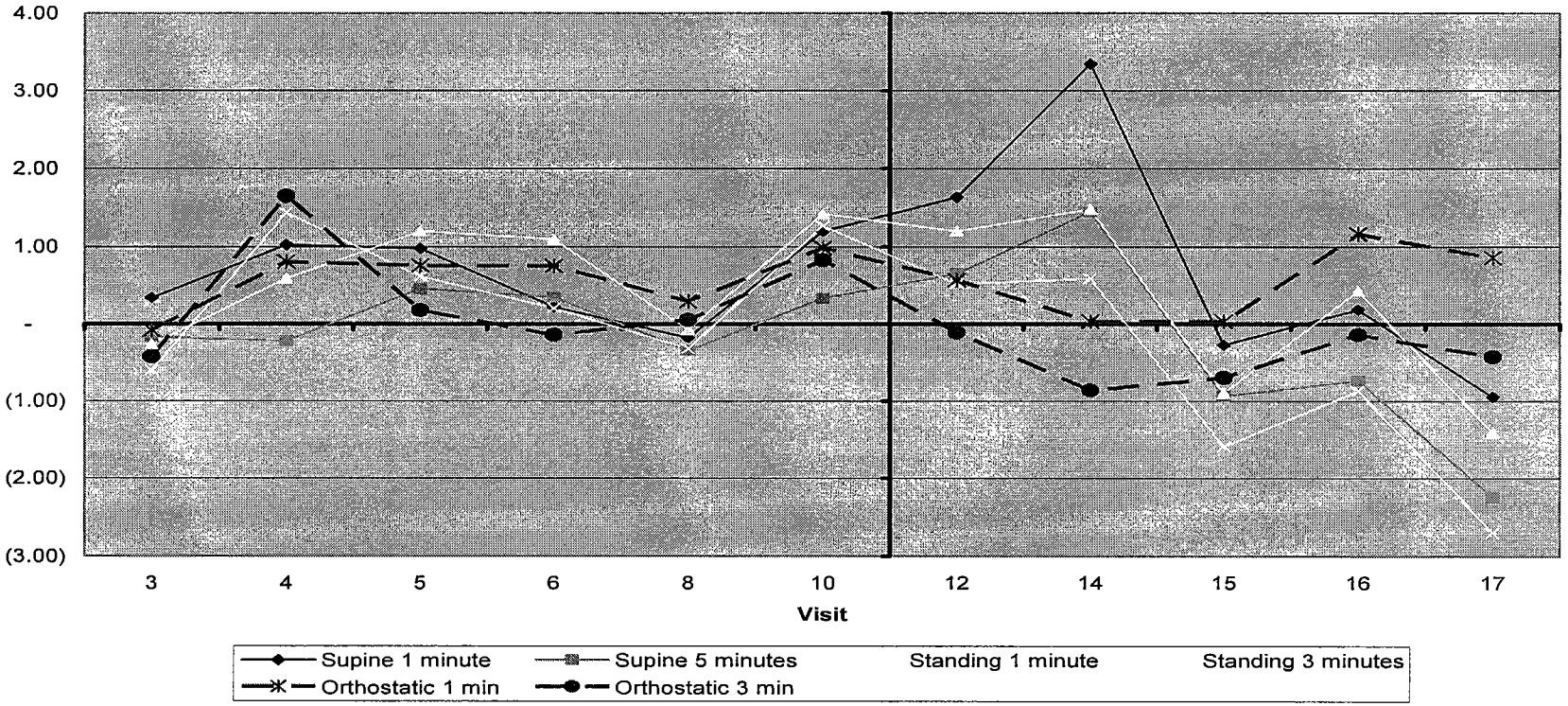
Note: The Y-axis divides the titration period from the maintenance period.

Figure 7.1.8.4.1.3
Change in DBP Relative to Placebo
SP512



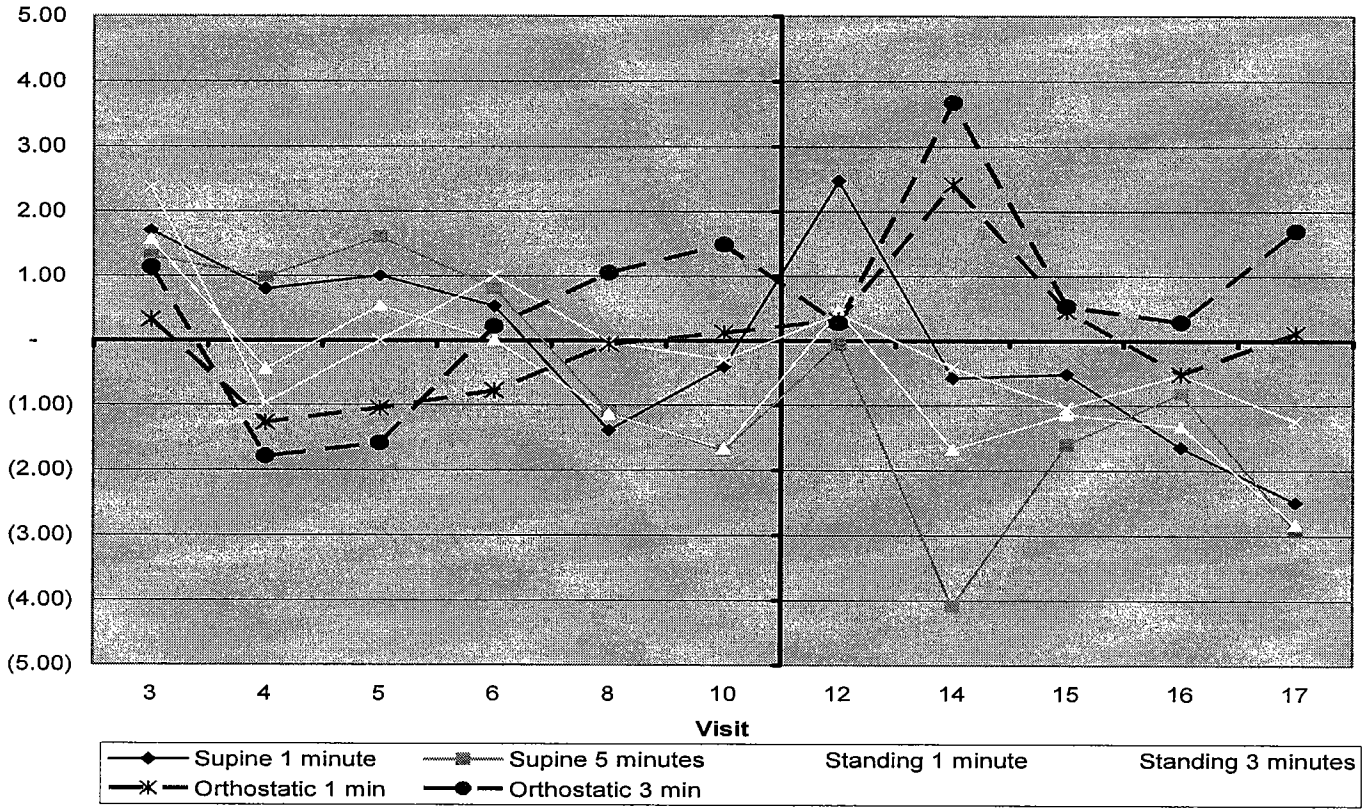
Note: The Y-axis divides the titration period from the maintenance period.

Figure 7.1.8.4.1.4
Change in Heart Rate Relative to Placebo
SP513



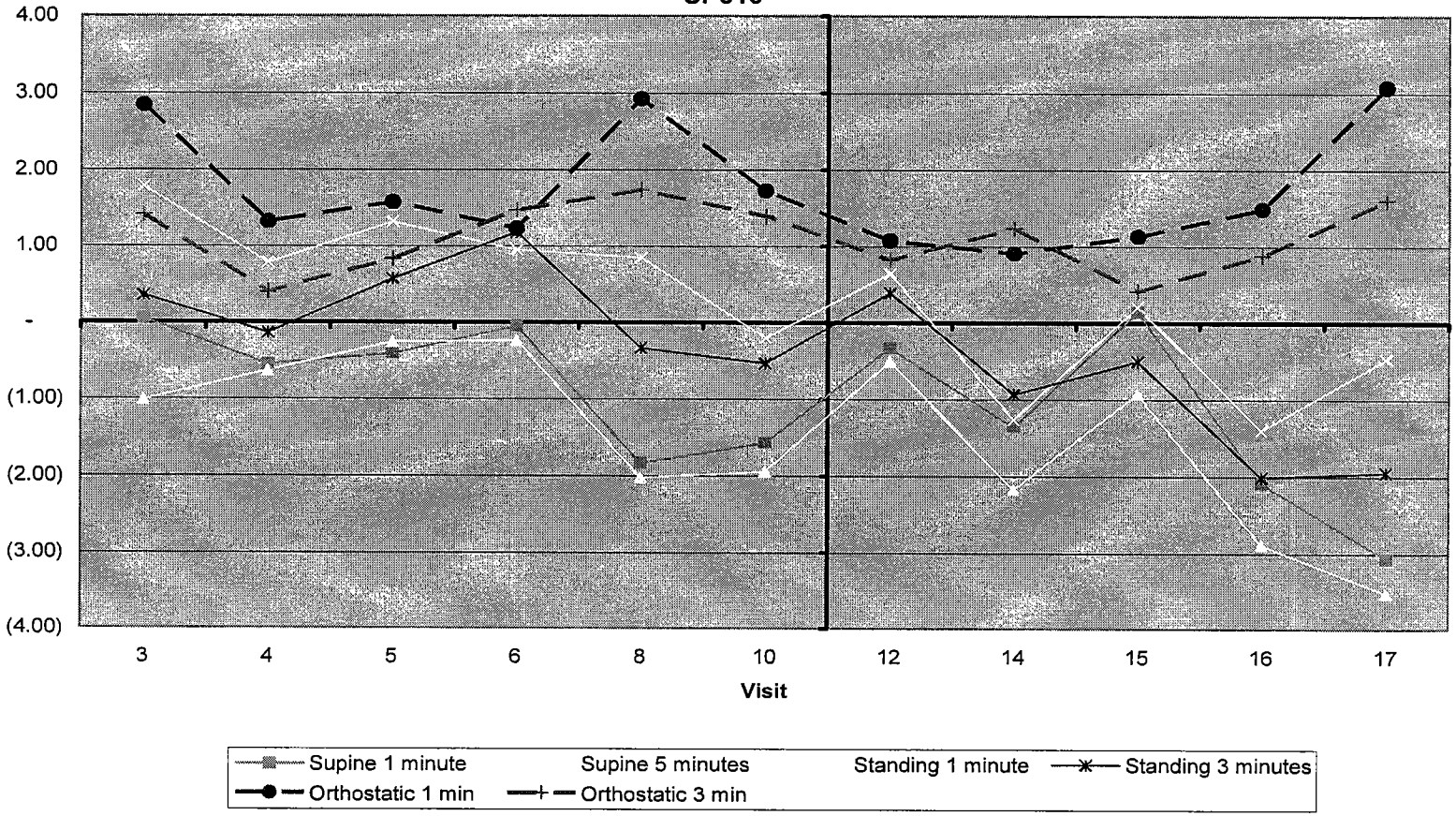
Note: The Y-axis divides the titration period from the maintenance period.

Figure 7.1.8.4.1.5
Change in SBP Relative to Placebo
SP513



Note: The Y-axis divides the titration period from the maintenance period.

Figure 7.1.8.4.1.6
Change in DBP Relative to Placebo
SP513



Note: The Y-axis divides the titration period from the maintenance period.

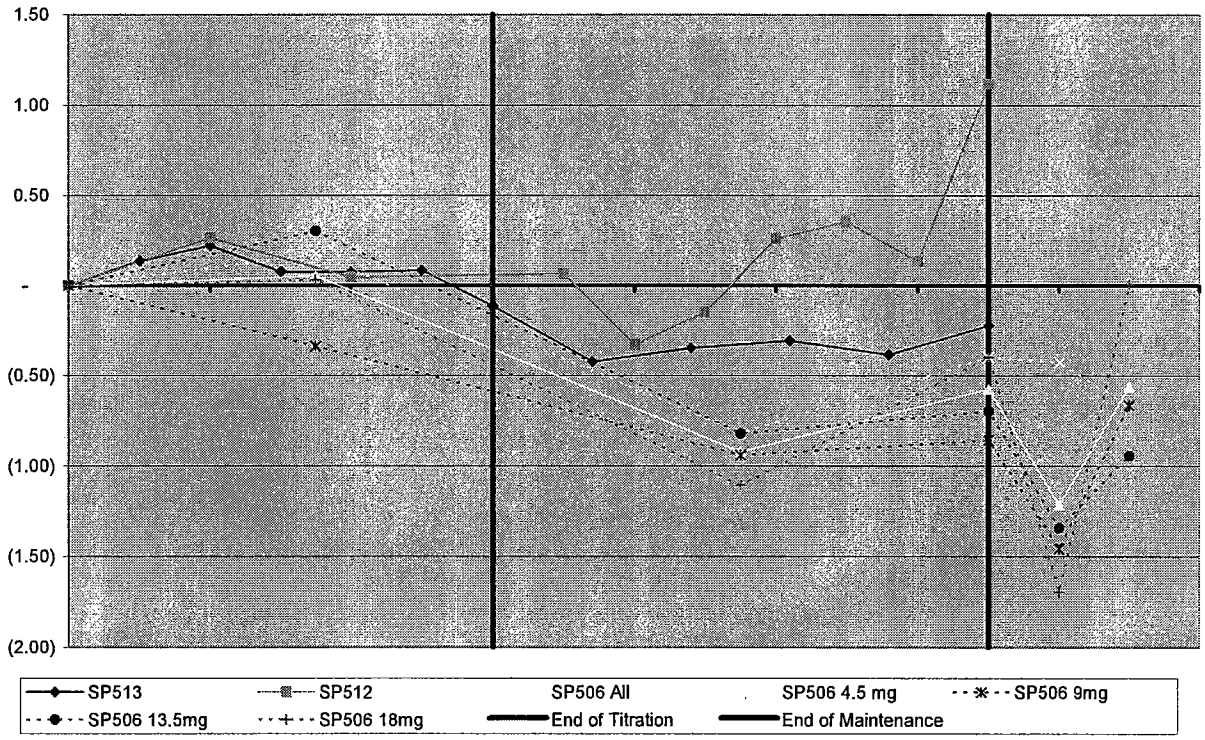
Reviewer's Table 7.1.8.4.1.4:
Summary of Mean Changes in Heart Rate and Blood Pressure

	SP506	SP512	SP513
Heart Rate			
Standing	+++	+++	++
Supine	++	+++	++
Orthostatic	++	**0**	+
Systolic Blood Pressure			
Standing	-	**0**	-
Supine	+	--	-
Orthostatic	-	++	**0**
Diastolic Blood Pressure			
Standing	+	--	--
Supine	++	---	---
Orthostatic	---	-	+++

The studies are most consistent in showing increases in both standing and supine heart rates with the increase in standing heart rates tending to be slightly greater, as reflected in a suggestion of an increase in orthostatic changes. Observed changes in blood pressure, particularly diastolic, do not show the same consistency. This can be explained by differences in the length of the treatment periods and by differences between fixed-dose and flexible dose studies. SP512 and SP513 have longer periods of observation than SP506. In the two longer studies, heart rate and blood pressure tend to decline over time, particularly toward the end of SP513. This could reflect acclimatization by subjects to an initial elevation of heart rate and blood pressure caused by rotigotine, a greater tendency for withdrawal from the study of subjects whose heart rate and blood pressure were increased by rotigotine or increasing use of beta-blockers and other antihypertensive treatments over time. Elevations of heart rate and blood pressure would also be more likely to be seen in the fixed-dose study if elevations were more likely to occur in subjects who receive higher doses of rotigotine than those necessary to achieve therapeutic effect.

Average changes in weight relative to placebo are shown in Reviewer's Figure 7.1.8.4.1.7. It should be noted in this figure, there is no time unit shown on the X axis because the duration of the titration and maintenance phases varied by study. All studies show a decline in weight at the beginning of the maintenance period that is reversed in SP513 but not in the other two studies. Weight loss was greater in SP506 and largely corresponded to dosage.

Figure 7.1.8.4.1.7
Weight Change Relative to Placebo



7.1.7.8.2 Analyses focused on outliers or shifts from normal to abnormal

The proportion of subjects in placebo and rotigotine groups in each principal study who crossed various threshold values is shown in Reviewer's Table 7.1.8.4.1.5. In order to combine the results of all three trials and assess statistical significance, negative binomial regression was used to calculate the incidence rate ratio for observations crossing a threshold for rotigotine relative to placebo, controlling for trial and the number of observations made. To provide additional information concerning the presence or absence of a dose-response relationship, logistic regression was performed on the SP506 results comparing dosage with the likelihood of crossing a threshold. Those logistic regressions showing some evidence of a dose-response are listed in the table with the odds ratio calculated for a 9 mg dose and p-value.

The results show that rotigotine subjects were more likely to experience tachycardia and less likely to experience bradycardia or a decrease in heart rate from baseline of more than 15 bpm. Rotigotine subjects were also more likely to have systolic blood pressures of more than 180 mmHg and increases of more than 40 mmHg over baseline. They were also more likely to see *decreases* in systolic blood pressure of more than 40 mmHg. Rotigotine appeared more likely to cause increases in diastolic blood pressure beyond 105 mmHg or more than 20 mmHg over baseline. Diastolic blood pressures of less than 50 mmHg were less likely with rotigotine. The influence may have been greater on standing diastolic blood pressure; positive orthostatic

changes relative to baseline were more common with rotigotine. There was less evidence for decreases in diastolic blood pressure than was seen for systolic blood pressure; only a small but significant increase in the probability of a 10 mmHg decrease in supine diastolic blood pressure could be demonstrated. An increase in weight of more than 10% over baseline was seen more frequently in rotigotine subjects. A decrease of 10% was also more likely; although less consistently observed across trials, the dose-response effect observed in SP506 was quite strong.

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Reviewer's Table 7.1.8.4.1.5: Incidence of Extreme Vital Sign Values

	SP506		SP512		SP513		All Studies				SP506 dose-resp.	
	Placebo	Rotigotine	Placebo	Rotigotine	Placebo	Rotigotine	IRR	[95%Conf. Interval]		p-value	OR(9mg)	p-value
Heart Rate												
Standing or Supine												
>100 bpm	2.9%	3.1%	8.4%	10.6%	10.2%	14.0%	1.29	1.17	1.43	<0.001		
<50 bpm	2.9%	2.6%	6.3%	5.0%	3.4%	2.8%	0.83	0.77	0.89	<0.001		
decrease >15 bpm	14.4%	10.5%	33.7%	27.9%	25.4%	24.7%	0.86	0.75	0.99	0.042	0.67	0.098
Standing												
>100 bpm	1.0%	0.4%	8.4%	10.6%	9.3%	14.0%	1.35	1.13	1.61	0.001		
decrease >15 bpm	19.2%	10.5%	24.2%	19.0%	18.8%	18.3%	0.77	0.56	1.05	0.097	0.53	0.008
Supine												
>100 bpm	2.9%	2.6%	1.1%	4.5%	2.5%	4.2%	1.69	0.83	3.44	0.148		
<50 bpm	2.9%	2.6%	6.3%	5.0%	2.5%	2.3%	0.85	0.77	0.94	0.002		
Systolic Blood Pressure												
Standing or Supine												
>180 mmHg	0.0%	4.4%	2.1%	2.8%	2.5%	4.2%	2.45	0.81	7.45	0.113	2.73	0.035
increase > 40 mmHg	4.8%	5.7%	2.1%	7.3%	4.2%	4.7%	1.52	0.82	2.82	0.183		
decrease > 40 mmHg	2.9%	5.2%	6.3%	5.6%	4.2%	9.3%	1.55	0.88	2.74	0.130		
Standing												
>180 mmHg	0.0%	3.5%	2.1%	2.8%	1.7%	3.3%	2.56	0.87	7.55	0.089	2.57	0.071
decrease > 20 mmHg	20.2%	18.8%	36.8%	33.5%	34.7%	30.2%	0.90	0.86	0.93	<0.001	0.75	0.136
decrease > 40 mmHg	1.9%	4.8%	4.2%	3.4%	2.5%	6.5%	1.77	0.86	3.62	0.121		
Supine												
>180 mmHg	0.0%	3.1%	2.1%	2.8%	2.5%	3.3%	1.96	0.73	5.26	0.183	2.13	0.156
decrease > 40 mmHg	1.0%	3.1%	2.1%	3.9%	2.5%	4.7%	2.07	1.58	2.72	<0.001		
increase > 40 mmHg	1.0%	4.4%	1.1%	4.5%	2.5%	2.3%	2.32	0.81	6.68	0.117	1.26	0.196

	SP506		SP512		SP513		All Studies				SP506 dose-resp.	
	Placebo	Rotigotine	Placebo	Rotigotine	Placebo	Rotigotine	IRR	[95%Conf. Interval]		p-value	OR(9mg)	p-value
Diastolic Blood Pressure												
Standing or Supine												
>105 mmHg	2.9%	6.1%	3.2%	7.3%	8.5%	12.6%	1.76	1.32	2.34	<0.001		
<50mmHg	0.0%	0.4%	2.1%	1.1%	1.7%	0.0%	0.39	0.09	1.68	0.207		
increase > 20 mmHg	6.7%	9.6%	11.6%	11.7%	9.3%	12.6%	1.24	1.01	1.52	0.037	1.41	0.177
Standing												
>105 mmHg	2.9%	6.1%	3.2%	7.3%	5.9%	10.7%	1.99	1.71	2.32	<0.001		
<50mmHg	0.0%	0.4%	2.1%	1.1%	1.7%	0.0%	0.39	0.09	1.68	0.207		
increase > 20 mmHg	4.8%	5.2%	5.3%	8.4%	6.8%	10.2%	1.41	1.16	1.71	<0.001	1.66	0.126
Supine												
>105 mmHg	2.9%	3.1%	2.1%	4.5%	4.2%	8.8%	1.78	1.22	2.59	0.003		
<50mmHg	0.0%	0.0%	1.1%	0.0%	0.0%	0.0%	0.00	0.00	0.00	<0.001		
increase > 20 mmHg	2.9%	6.6%	9.5%	8.4%	6.8%	7.0%	1.16	0.74	1.82	0.523	1.52	0.011
decrease > 10 mmHg	21.2%	22.3%	37.9%	43.0%	38.1%	45.1%	1.14	1.07	1.20	<0.001		
Orthostatic Changes												
increase > 10 mmHg	28.8%	31.0%	31.6%	36.9%	28.0%	35.3%	1.17	1.07	1.28	0.001		
increase > 20 mmHg	2.9%	2.6%	5.3%	8.4%	3.4%	7.9%	1.66	1.08	2.55	0.021	0.47	0.152
Weight												
increase > 10%	2.9%	3.9%	3.2%	6.7%	0.8%	0.9%	1.65	1.15	2.37	0.007	1.85	0.123
decrease > 10%	1.9%	4.8%	4.2%	3.4%	1.7%	2.8%	1.44	0.72	2.91	0.304	2.45	0.027

Reviewer's Conclusions and Recommendations

1. The analyses presented here clearly establish that rotigotine on average increases heart rate and increases the incidence of tachycardia although the frequency of large increases in heart rate do not appear increased. This could be of clinical importance in patients with coronary artery disease or congestive heart failure and should be listed in [redacted] abeling [redacted]
2. The overall effect on blood pressure is less clear but it appears likely that rotigotine can increase the likelihood of substantial increases or decreases in blood pressure. The Sponsor's proposed labeling [redacted]
3. No significant impact by rotigotine on postural changes in heart rate or blood pressure was observed.
4. 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?

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Background

Preclinical *in vitro* studies of rotigotine in papillary muscles isolated from guinea pig hearts and Purkinje fibers isolated from canine hearts showed increases in action potential duration at 90% repolarization at concentrations of 100 nM. Neither arrhythmia nor early after-depolarizations were observed in any of these preparations. In vitro human ether-a-go-go related gene (hERG) channel testing revealed that rotigotine affected the hERG-mediated potassium current with an IC_{50} of 150 nM. Preclinical cardiovascular effects were studied in anesthetized monkeys and no statistically significant effects on blood pressure, heart rate, or electrocardiogram intervals were detected up to 4.0mg/kg of rotigotine administered subcutaneously.

Electrocardiographic (ECG) monitoring in one of three early trials of intravenous rotigotine (N-0923/006) showed that three of eight subjects had an increase in the

frequency of asymptomatic ventricular extrasystoles during drug administration and one subject had an isolated episode of asymptomatic, non-sustained, ventricular tachycardia. On review of the ECG data from all three intravenous trials a relationship between rotigotine treatment and cardiac rhythm disturbances could not be excluded with certainty.

ECG Collection in Studies of Transdermal Rotigotine
In Phase 1 trials of transdermal rotigotine (TD-0923-001, TD-0923-003, SP502, SP503, SP581, SP606, SP610, SP626, SP627, SP596, SP717, SP718, SP628, SP629, SP673, SP670, SP671, SP672), 12-lead ECGs and rhythm traces were recorded with local ECG equipment at 25mm/sec and 50mm/sec paper speed, respectively, on 8- to 10-second strips. In addition to 12-lead ECGs, a Holter ECG was also recorded on a — . tape recorder in SP503. The original hardcopy ECG traces were shipped to the core ECG laboratory and analyzed by qualified cardiologists, blinded to subject and trial information.

For the Phase 2 trials, 12-lead ECGs were obtained with either local ECG equipment as in Phase 1 for SP534 Parts 1 and 2 and SP535. Trials SP506, SP511, SP591 and SP540 used digital transtelephonic equipment that transmitted electronically to the core ECG laboratory where ECGs were read manually at computer workstations.

For the Phase 3 trials, SP512 and SP513, standard 12-lead ECGs were taken pre-treatment, during titration (SP513DB only), at the end of titration (SP512DB only), at the commencement of the maintenance phase, after 12 and 24 weeks of the maintenance phase, and at the safety follow-up assessment. An ECG was also to be performed in the event that a subject was prematurely withdrawn from the trial (withdrawal assessment). Prior to the commencement of dose escalation (Visit 2), 3 separate 12-lead ECGs were taken at least 15 minutes apart to calculate the average QTc value (baseline). The ECGs were read locally by the investigator or qualified designated reader who then signed and dated their assessment. Changes in ECG parameters were relative to baseline, which was considered to be the Visit 2 ECG. The investigator confirmed the computerized measurements of PR, QRS, QT and QTcB intervals (assessed as the mean of 3-5 beats).

Per request by FDA at the pre-NDA meeting (post hoc to the trial), all ECGs in the pivotal trials (SP 506, SP512 and SP513) were centrally read (— . in order to maximize the reliability of the data. All 12-lead ECGs were reviewed in a blinded fashion by one qualified cardiologist. Interval measurements were performed using a digital on- screen system. Final values were determined from a combination of multiple measurements derived from the placement of markers at the onset and offset of intervals of the individual complexes. Duration values were electronically determined from the annotation points and combined by software systems to produce final results. Measurements included heart rate, rate/range, PR, QRS interval, QT interval, QRS axis, ST morphology, T-wave morphology, and U-wave presence. Standard full diagnostic ECG interpretation were provided including corresponding criteria, diagnostic statements and severity code corresponding to probable clinical relevance.

For the dedicated QT study (SP 630), ECGs were obtained digitally using a — — ECG continuous recorder. The ECGs were stored on a flashcard about every 10 seconds. They were read centrally by cardiologists (2 cardiologists). Three 12-lead ECGs were downloaded from the — flashcard at each of the following matched time points on Days -1, 27, and 30: 0, 1, 2, 4, 5, 6, 7, 8, 10, 12, 14, 16, 18, 20, 22, 23:30 hours. On Days 25, 26, 28, and 29, 3 ECGs were downloaded at 0 (pre patch application), and 4, 8, and 12 hours post patch application. Plasma samples for determination of rotigotine concentrations and pharmacokinetic analysis were drawn at the same time points as the ECGs on Days 25 through 30.

For both paper and digital ECG data analysis only manual measurements were considered. The QT interval was measured, wherever possible, from the same lead of each ECG (limb lead II by convention). The QT interval was defined from the earliest onset of the QRS complex to the latest offset of the T wave. Leads in which these points were not clearly discernible were excluded from analysis. The ST segment was defined as the segment between the end of the QRS complex (J point) and the beginning of the T wave. The U wave is the low frequency deflection at the end of the T wave. U waves were not included in QT interval measurement, unless the T and U waves merged to produce a morphologically single TU wave.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Twelve clinical studies of transdermal rotigotine collected substantial ECG data.

Phase 1

SP502

Study SP502 was a single-center, open-label, single administration with randomization to crossover using different forms of transdermal patch. Fourteen healthy, male volunteers aged 18 - 50 years were enrolled, twelve of whom completed the trial. ECGs and plasma rotigotine levels were obtained at screening, pre-trial, prior to patch application and (at 4, 12, 24, 28 and 48 hours post application) at each of the three trial visits and at the safety follow-up visit. Initially, change in Bazett-adjusted QT interval from baseline and Bazett-adjusted QT intervals derived from automated readings were plotted against plasma concentrations of rotigotine. This analysis showed a positive and statistically significant relationship between QT interval and rotigotine concentration.

Because of these findings, the sponsor commissioned an additional analysis of the ECG data from this study that criticized the original analysis for not accounting for the contribution of several data points from each subject (confounding within- and between-subject variability), using only the Bazett correction that overcorrects (produces longer QT intervals) at higher heart rates and using automated readings that were considered unreliable. A revised analysis consisted of linear regression models derived, using the manually calculated ECG parameters only, for all subjects completing the trial. The RR interval, the unadjusted QT interval, the QTc and the change (shift) from baseline of all these parameters were plotted against plasma concentrations, and against the RR interval

over all time points and treatments (except where specified). This produced QT:RR slopes for each subject, and the mean slope over all subjects was then tested against the hypothesis that the mean slope should have been zero (i.e. that the explanatory variable has no relationship to the dependent variable) using a two-tailed t-test. For the shift plots, the screening and post-treatment data points were excluded, and shifts were calculated from the baseline measurement of the relevant visit. For shift plots against plasma concentration and against RR shift, the regression lines were forced through the origin. For the plots against RR, an additional set of plots and regressions was derived in which the data points were restricted to drug-free measurements (i.e. screening, baseline and post-treatment measurements) calculating the slope of the relationship between rotigotine concentration and QT interval and change in QT interval using no correction and the Framingham, Fridericia and Bazett corrections.

Reviewer Comment: The criticism of the initial analysis is valid but does not explicitly discuss a broader problem: the relationship between QT and plasma rotigotine may be very different among subjects than it is within individual subjects. The epidemiological literature refers to this problem as the ecological fallacy. However, the revised analysis using individual slopes is also problematic. Although some subjects may show a strong linear relationship between QT and plasma concentration, in others the correlation may be poor. Unfortunately, this method gives equal weight to all subjects. This is particularly troublesome when there are subjects with little variability in either rotigotine concentration or QT interval. Depending on whether QT interval or rotigotine concentration is modeled as the x-axis (independent) variable, these subjects will have slopes calculated that are either close to zero (a horizontal line) or of very large magnitude (a nearly vertical line). Near-vertical lines will have either very positive or very negative slopes depending on slight differences in the data. In a simple average of slopes, these nearly vertical lines will have excessive influence on the calculation the mean and standard deviation of the slopes, invalidating the t-test.

SP503
This was a single center, open label, placebo run-in, non-randomized, multiple dose administration trial. Thirty healthy male volunteers received placebo patch on days 1 and 2, then active drug patch (4.5mg/10cm2) on days 3 to 16. Multiple ECGs and plasma rotigotine concentrations were recorded daily throughout the treatment period. Analysis of the relationship between rotigotine concentration and QT interval were done using the same averaging of slope method used in SP502.

Phase 2
SP511
This was a multicenter, double-blind, randomized, placebo-controlled, 4-arm, parallel-group trial of rotigotine in over 300 subjects with advanced stage idiopathic PD. A total of 324 subjects were randomized to 1 of 3 target doses of active drug (9.0, 18.0 or 27.0mg rotigotine) or placebo and 322 subjects were treated. ECGs were obtained at screening, pre-treatment run-in period, baseline evaluation, titration and maintenance periods. ECGs were also recorded at the safety follow-up visit. Plasma rotigotine levels