Review and Evaluation of Clinical Data

Safety Review

Application Information

NDA 20-658

Smith Kline Beecham

Clock Date: January 2, 1997

Drug Name

Generic: Ropinirole hydrochloride

Proposed Trade Name: Requip

Drug Characteristics

Pharmacological Category: Dopamine agonist

Proposed Indications: 1) Primary symptomatic treatment of Parkinson's disease.
2) Adjunctive treatment of Parkinson's disease.

Dosage Forms: Oral tablets in 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg

Proposed Use:

Ropinirole should be given T.I.D. using a 4 week dose escalation scheme as follows: 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D. After 4 weeks, dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis up to 24 mg per day. Withdrawal should occur gradually over a 7-day period.

Safety Reviewers: Greg Burkhart, M.D., M.S., James Knudsen, M.D., Ph.D.

Date of Review: October 11, 1996

1 Summary of Ropinirole Safety Review

SKB is requesting approval to market ropinirole for both early treatment (ET) and adjunctive treatment (AT) of Parkinson's disease (PD). Overall, the ISS summarized the safety experience for 515 ET and 849 AT patients with each having about 514 and 651 person-years (PYs) of ropinirole use, respectively. Both ET and AT patients had over 100 PYs of ropinirole use that occurred after the first year of use. There were 79 ET and 97 AT patients who reached 24 mg/day, the maximum recommended daily dose. Of these 176 patients, 124 were exposed to 24 mg/day for at least 12 weeks.

In clinical pharmacology studies, ropinirole had significant cardiovascular (CV) effects on healthy volunteers. Ropinirole caused a consistent dose related reduction in standing BP at 1 and 2 hours post-dose when compared to placebo. At 1 hour following a 1 mg dose, the mean decreases of standing systolic and diastolic BP were 15 and 10 mm Hg, respectively. The effect of ropinirole on standing pulse was not as consistent. After a 1 mg dose, the mean standing pulse decreased 8 beats per minute (bpm) at 1 hour, but at 2 hours, there was a mean increase of 15 bpm. While 47 PD patient volunteers were also included in phase 1 studies, the NDA did not clearly describe whether similar changes in BP and pulse were also observed in patient volunteers, and if so, at what doses. Of the 110 healthy volunteers, 9 had either orthostatic hypotension or were so symptomatic on standing that BP could not be measured. There were 2 similar events in patient volunteers. One healthy volunteer had full clinical recovery following orthostatic hypotension, syncope and 26 seconds of asystole that occurred 1 hour after a 1 mg dose when standing for a BP measurement. Ropinirole also caused a small clinically insignificant increase in resting supine heart rate, decreased uric acid secretion, decreased serum prolactin, nausea, dizziness and somnolence. Ropinirole did not prolong the QT interval or cause any evidence of dysrhythmia other than the bradycardia that was observed 1 hour post-dose and in 8 of 9 patients who were orthostatic.

Significant differences in design between US and non-US phase 2/3 studies necessitated individual review of US studies to adequately describe ropinirole associated AEs. In the US ET study (054), the frequency of study dropout associated with either serious or non-serious AEs, was about 2 fold greater with ropinirole than placebo. The difference between ropinirole and placebo in the frequency of study dropout was mostly explained by differences occurring between 10 and 20 weeks of study. This period generally corresponded to doses equal to or greater than 4.5 mg per day. The three most common AEs associated with dropout in study 054 were nausea, dizziness and syncope. The risk of serious AEs was also about 2 times as frequent with ropinirole than placebo. Six of these 22 serious AEs in study 054 were CV in nature with several patients hospitalized following syncope and/or orthostatic hypotension. Nausea, somnolence, fatigue, viral infections, abdominal pain, syncope, orthostatic hypotension, confusion and leg edema were reported in more than 5% of ropinirole patients and were at least 2 times more frequent than in placebo. Syncope had the largest relative difference in risk when compared to placebo; 10.3% (12 events) compared to 1.6% (2 events). While no objective evidence of orthostatic hypotension was observed, BP measurement was

not timed to last dose. There were no deaths in study 054, and across all ET patients in the ISS, the mortality rate with ropinirole was about 50% of that in other treatment groups.

In the US AT study (044), ropinirole exposure was not associated with increases in study dropout either overall or that associated with an AE, and not associated with an increased risk for serious AEs when compared to placebo. None of the 15 patients exposed to ropinirole who had serious AEs had syncope, bradycardia or orthostatic hypotension and only 1 patient had an event that could be considered CV in nature. There was no clear pattern of AEs that were associated with dropout. There were no deaths in ropinirole patients in study 044, and across all AT patients in the ISS, ropinirole mortality was less than that in any other treatment group. Across all AT placebo controlled studies in the ISS, dyskinesia, increased sweating, anxiety, tremor and confusion were reported in more than 5% of ropinirole patients and were at least 2 times more frequent than in placebo. Syncope was reported in 3.2% of ropinirole AT patients compared to 1.2% in placebo patients.

Across all patients exposed to ropinirole in the development program, there were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, aplastic anemia, or rhabdomyolysis. There were no significant shifts in any laboratory or ECG parameter from baseline to study endpoint. Two patients were hospitalized with poorly described serious skin reactions. Another patient developed life threatening thrombocytopenia that was purported to have an immune mechanism. Two patients developed renal failure that could have been secondary to underlying disease. One patient was lost to follow-up who had an undefined renal disorder.

In summary, ropinirole use in US ET patients was associated with increased risks for serious AEs and AE dropouts with the clinical nature of several of these AEs consistent with ropinirole's CV effects observed animals and in Phase 1 healthy volunteers. While there was a clear increase in CV events attributable to ropinirole in US ET patients, there were no deaths in study 054 and across the ISS, overall mortality was less with ropinirole than any other treatment group. While there was an increased risk for syncope and non-CV events in AT patients, ropinirole seemed to be better tolerated in AT patients. Considering the low prevalences of underlying CV disease and CV medication use in study 054, the labeling should warn that ropinirole has significant CV effects and that is has not been studied in patients who are both candidates for ET and who have moderate or severe CV disease. Such warning should also be considered for AT patients since study 044 also excluded patients who had moderate or severe CV disease. Phase 4 study of ropinirole's use in patients with underlying CV disease could delineate any increased risk.

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2 Background

2.1 Overview of Safety Review

SKB is requesting FDA approval to market ropinirole as primary therapy (referred in the NDA as early therapy {ET}) and as adjunctive therapy (AT) of Parkinson's disease (PD). Since the 2 populations identified by these indications could vary with respect to likelihood of background events because of differences in age, extent of underlying diseases and other factors, SKB provided separate descriptions of treatment emergent adverse events (AEs) in ET and AT patients in the integrated summary of safety (ISS).

In our evaluation of the safety experience with ropinirole, a similar approach was followed except that specific findings from the US ET study 054 and the US AT study 044 were also reviewed and discussed to provide contrast with the findings in the ISS. Separate discussion of studies 054 and 044 was necessary because the ISS combined US and non-US studies without considering the validity of such pooling in the face of significant differences in design.

Appendices 1, 2 and 3 provide SKB Tables from the ISS, 054 study report and 044 study report, respectively and are referred to in this review.

2.2 Development of Ropinirole

According to SKB, development of ropinirole as a treatment for PD was pursued because preclinical studies suggested that it had little affinity for dopamine-D1 and 5-HT1 receptors, and a dopamine-like affinity for dopamine D2 receptors. Based upon this preclinical receptor profile, SKB hypothesized that ropinirole would have advantages in efficacy and/or safety when compared to approved dopamine agonists. Ropinirole's clinical development program began in the UK with administration to healthy volunteers in July 1987. As of 1/1/96, ropinirole has not been marketed in other countries and there have been no foreign regulatory actions regarding its approval.

2.3 Ropinirole Preclinical Studies

According to SKB, bromocriptine and pergolide each has affinity for D1 and D2 receptor subtypes, 5HT1A receptors and adrenoreceptors, but ropinirole and its metabolites bound with high affinity to the central D2 dopamine receptors in human and rat tissue, but not to D1, b-adrenoreceptors, benzodiazepine, GABAA, 5-HT1, 5-HT2 or muscarinic receptors. Ropinirole bound with moderate affinity at opiate receptors and with low affinity at a-adrenoreceptors.

Single dose studies in the mouse and rat showed that the oral lethal dose ranged from

600-900 mg/kg. While there were no histological changes in these studies, the animals displayed hyperactivity, abnormal locomotion, stereotypy, tremors and convulsions.

General animal toxicity findings included decreases in arterial blood pressure, coronary blood flow and total peripheral resistance; general disturbance of motor activity (including behavioral changes); hypoprolactinemia, and general antidepressant activity. Many of these effects were reduced when ropinirole was co-administered with domperidone, a peripheral D2 blocker. There was no effect upon the respiratory or hematological systems, or liver. However, several animals at increased ropinirole doses developed petechial gastric hemorrhage.

In tilt testing, ropinirole caused significant orthostatic hypotension, which according to SKB, resulted from presynaptic inhibition of noradrenaline release effectively blocking the normal afferent noradrenergic response to tilt. This explanation was apparently based upon the relative and absolute bradycardia that was observed in some animals that developed excessive hypotension during tilt, and the reduced norepinephrine levels observed during ropinirole exposure. There was no evidence of QT prolongation or ventricular dysrhythmia observed in these studies and according to SKB, there was some degree of tolerance to the hypotensive effect.

Because of ropinirole's activity at the opiate receptors, SKB conducted animal studies to investigate any potential for withdrawal. In these studies, discontinuation of ropinirole did not result in withdrawal symptomatology nor did ropinirole ameliorate withdrawal caused by other agents. Carcinogenicity studies were interpreted by SKB as negative. The ropinirole-induced Leydig cell hyperplasia and testicular adenomas observed in rats were explained by reduced plasma prolactin that caused a reduction in Leydig cell LH receptors which are apparently not present in humans.

2.4 Review of Safety Issues Identified in SKB's Proposed Labeling

There were no warnings in the proposed labeling. Under the *Precautions* section, caution was recommended when initiating ropinirole because of its potential to cause symptomatic hypotension. Caution was generally recommended in all patients with severe underlying cardiovascular disease since such patients were not studied in the ropinirole development program. There was no description of the extent of underlying CV disease that would be consistent with "severe". The labeling also states that ropinirole should not be used in patients with major psychotic disorders such as schizophrenia and it warned about operating motor vehicle or heavy machinery at the start of ropinirole therapy because of somnolence.

Under the AE section of labeling, 17.1% and 17.3% of ET and AT patients dropped out of study associated with AE occurrence. These AE dropout risk estimates included

all US and non-US experience and estimates were not given for placebo ET or AT patients. In ET patients, nausea (4.1%) was the most common reason for withdrawal while in AT patients, hallucination (3.2%) was the most common reason. The AE section also states that the incidence of orthostatic hypotension was no different with ropinirole than with placebo and that, while ergoline derivatives have been associated with retroperitoneal fibrosis and other rare events, such events were not observed with ropinirole.

Table 1 provides a summary of AE risk estimates that were listed in the AE section of the proposed labeling that were observed in randomized placebo controlled ET studies (Table 2 in proposed labeling). In table 1, events are listed if they occurred in more than 3% of the ET patients where the event rate was more than 2 fold greater than placebo. Interestingly, the cumulative incidence of syncope was 8.2 times greater during ropinirole use than with placebo, and although there are many non-CV causes of syncope, the validity of SKB's statement that there were no objective cases of orthostatic hypotension requires careful review. In addition to increased risk of syncope, somnolence, hallucination, and confusion that was associated with ropinirole's use, peripheral ischemia, general GI symptomatology and undefined ocular findings were also increased with ropinirole.

Table 1. Adverse events that occurred in more than 3% of and were more than 2 fold greater in ropinirole ET patients than with placebo.
(Taken from Table 2 of sponsor's proposed labeling which uses data from studies 054 and 032.)

	Ropinirole		Placebo	
	N=157	%	N=147	%
Flushing	5	3.2	1	0.7
Asthenia	10	6.4	2	1.4
Edema Legs	10	6.4	1	0.7
Fatigue	17	10.8	6	4.1
Malaise	5	3.2	1	0.7
Syncope	18	11.5	2	1.4
Abdominal Pain	10	6.4	4	2.7
Anorexia	6	3.8	2	1.4
Dyspepsia	15	9.6	7	4.8

Nausea	94	59.9	32	21.8
Confusion	8	5.1	2	1.4
Hallucination	8	5.1	2	1.4
Somnolence	62	39.5	9	6.1
Yawning	5	3.2	0	0.0
Infection Viral	17	10.8	5	3.4
Dyspnea	5	3.2	0	0.0
Peripheral Ischemia	4	2.5	0	0.0
Eye Abnormality	5	3.2	2	1.4

Table 2 uses the same selection criteria as Table 1 and is also taken from SKB's proposed labeling. Overall, there were fewer AEs that were significantly associated with ropinirole use in AT patients. The most common AE associated with ropinirole use was dyskinesia. Events coded as confusion and/or amnesia had the largest relative differences from placebo. As in ET patients, the risk of syncope was increased with ropinirole compared to placebo, but neither the absolute or attributable risk was as high as that observed in ET patients.

Table 2. Adverse events that occurred in more than 3% of and were more than 2 fold greater in ropinirole AT patients than with placebo.
(Taken from Table 3 of sponsor's proposed labeling.)

	N=298	%	N=151	%
Mouth Dry	13	4.4	2	1.3
Sweating Increased	17	5.7	2	1.3
Syncope	10	3.4	2	1.3
Dyskinesia	85	28.5	19	12.6
Paresthesia	13	4.4	3	2.0
Tremor	17	5.7	4	2.6
Amnesia	10	3.4	1	0.7
Anxiety	17	5.7	3	2.0

Confusion	20	6.7	2	1.3
Nervousness	12	4.0	3	2.0

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3 Methods of Safety Review

Using both the paper and electronic versions of the NDA, treatment emergent AEs occurring with ropinirole use were evaluated separately in ET and AT patients as follows. To verify the accuracy of the primary data that was summarized in the NDA, given the data that was available for review, information listed in the data listings, CRFs and death narratives were cross checked for accuracy. To evaluate the reasonableness of the AE coding (WHOART), subsumed investigator verbatims were generally compared to the corresponding preferred WHOART AE code. To examine the validity of AE coding further, selected WHOART codes were reviewed in more detail. These codes were implicitly selected based upon the AE description in the proposed labeling, toxicity findings from preclinical testing and findings noted during the NDA review. In particular, any supporting data for patients coded with the WHOARTs "orthostatic hypotension", "ataxia", "postural instability" and "bradycardia", were reviewed focusing on evidence of hypotensive or general CV events. All investigator verbatims for CV WHOART codes in US studies 054 and 044 were also reviewed to evaluate their specificity. As noted in section 4.3 below, SKB enhanced the code, "orthostatic hypotension" by including events that were postural in character, but without any documented change in BP.

Since deaths were observed in RCTs before patients entered extensions, ropinirole mortality was compared to that in comparison groups separately for ET and AT patients. Ropinirole mortality rates in ET and AT patients were also compared to that observed during placebo and bromocriptine. For the rate comparison, person-years (PYs) were estimated from the ISS summary tables showing the number of patients in study by 3 month time intervals. Patients withdrawing or completing study during a 3 month interval were assumed to contribute 1.5 months. In addition to describing the mortality risks and rates, case summaries of all sudden or CV deaths were prepared by extracting data from the CRFs, narrative summaries and CRF tabulations. In addition, the CRFs, narrative summaries and data tabulations were reviewed for the following groups of patients: (1) serious AEs (2) AEs associated with dropout (3) AEs coded as syncope, bradycardia, ventricular tachycardia/fibrillation or peripheral ischemia and (4) patients with any AEs suggestive of agranulocytosis, aplastic anemia, thrombocytopenia, serious skin reactions such as Steven's Johnson Syndrome, hepatic failure or necrosis, renal failure or worsening of renal function, rhabdomyolysis, urolithiasis, hematuria or urosepsis, retroperitoneal fibrosis or pulmonary fibrosis.

Since justification for pooling of the US and non-US data was not provided in the ISS with clear differences in design (discussed more in section 4.1), the AE experience observed in the US study 054 (ET patients) and 044 (AT patients) was contrasted to that provided in the ISS. The review of studies 054 and 044 focused on deaths, serious AEs, dropout risk, dropouts associated with AE occurrence and common AEs. In describing

variation in dropout risk by time since start of study, risk was estimated for each week of study using data available in the study reports provided in the NDA.

Because SKB focused on absolute risk and not either relative or attributable risk in describing the effect of concurrent medications, demographic subgroups or underlying diseases on attributable ropinirole risk, RRs were calculated from SKB tables for seligiline use, HCTZ use, gender, age category and hypertension.

4 Review Findings

4.1 Description of the Ropinirole Development Program

The ISS described ropinirole treatment emergent AEs based upon observations from 11 clinical pharmacology studies conducted in healthy volunteers, 5 clinical pharmacology studies conducted in PD patients[1], 25 therapeutic and 2 compassionate use studies. SKB Table 2.1[2] provides a listing of all studies included in the ISS. The ISS-excluded AEs observed from 2 Japanese studies - a clinical pharmacology study in healthy volunteers and an open phase 2 study. A summary of the AEs observed in these 2 studies was provided in the NDA although it was not detailed in scope.

Most phase 2/3 studies seem to have been conducted entirely in the US or were entirely foreign in conduct. Studies 054 (ET patients) and 044 (AT patients) were the only studies conducted in the US. In addition to being placebo controlled, both had subsequent extensions.

The phase 2/3 studies summarized in the ISS included the following comparative designs. In ET patients, there were 2 placebo controlled studies (032 and 054) and 2 comparative studies, 1 against l-dopa (056) and the other against bromocriptine (053). In AT patients, there were 3 placebo controlled studies (030, 034 and 044), and 1 comparative study against bromocriptine (043).

There were significant differences in design between the US studies (054 and 044), and the foreign studies. Such differences could cause differing background AE rates, and if present, preclude combining US and non-US safety data. The most significant difference may have been in the extent of exclusion criteria applied in US studies. In

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[1] Although difficult to determine, it appears that most of the PD patients included in the clinical pharmacology studies can be classified as AT patients.

[2] Appendix 1 contains all SKB tables that are referred to in this review that are from the ISS. Appendix 2 contains SKB tables from the 054 study report. Appendix 3 contains SKB tables from the 044 study report.

US studies 054 and 044, patients were excluded if they were taking any of the following cardiovascular medications within 2 weeks baseline: vasodilators (other than short-acting nitrates), antiarrhythmics, digoxin, beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors or other anti-hypertensive agents (excluding diuretics). Because of such differential exclusion, patients in 054 and 044 probably had lower prevalence of underlying CVD than in foreign studies. Theoretically, a lower CVD prevalence could result in lower background AE rates for CV events in US patients. Given a such a difference, combining data across US and non-US studies could bias the description of AEs observed in US patients.[3] Of course, excluding patients with CVD could also remove patients who are more susceptible to any CV effects of ropinirole.

A second difference between US and non-US studies was that US patients were randomly assigned treatment stratified on selegiline use while non-US studies allowed selegiline use to occur based upon investigator practice. If concurrent use of selegiline and ropinirole was associated with a different level of AE risk than ropinirole alone, and US and non-US studies differed in their extent of selegiline use (which seems likely), then biased risk estimates in US patients could also occur when pooling. Finally non-US sites could also use domperidone to control symptoms such nausea, vomiting, somnolence and orthostasis, which if effective and the data are pooled, could again cause biased risk estimates in US patients.

There were some other changes in the development program that may be worth noting. In the more recent studies, the dose escalation schedule was changed to start at a lower daily dose (0.25 instead of 0.5 mg) that was given T.I.D. instead of B.I.D. This change was reportedly made because of evidence in latter PK studies conducted in PD patients that the half-life was 6 hours and not 8 hours as observed in healthy volunteers. Another minor change occurred for the US ET study (054) where the protocol was amended to allow rescue with Sinemet and/or Sinemet CR according to the investigator's standard practice.

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[3]For example, assume that in non-US studies the chest pain risk is 15% with ropinirole and 10% with placebo, and in US studies the risk is 6% with ropinirole and 1% with placebo. The risk attributable to ropinirole is the same but the relative risk (RR) is several fold greater in US patients providing more compelling evidence that ropinirole was causally related to the occurrence of chest pain in US patients. Assuming that the number patients are equal in each group, the risks pooled across US and non-US studies would be 10.5% with ropinirole and 5.5% with placebo providing a valid estimate of the attributable risk, but understating the RR in US patients. Epistemologically, the RR is considered more important in defining causal events than attributable risk, though the latter is more useful for evaluating the public health impact of the event.

The dose escalation that was followed in the US studies and the more recent non-US studies is shown below. All patients started on the first dose level (0.25 mg t.i.d.) of study medication and received weekly increases until an optimal dose was achieved. However, all patients continuing in the studies had to be titrated to a minimum dose level 5 (1.5 mg t.i.d.) which could have been achieved by week 5 if study drug was tolerated. Titration above dose level 5 was made based upon therapeutic response and patients could then be maintained on the optimal dose level for the remainder of the study. The maximum dose was 8 mg t.i.d. (dose level 13). For patients discontinuing ropinirole, tapering of ropinirole occurred over a 1 week period.

Dose Level	Ropinirole	L-dopa	Bromocriptine
1	0.75 mg	50 mg	1.25 mg
2	1.5 mg	100 mg	2.5 mg
3	2.25 mg	150 mg	5.0 mg
4	3.0 mg	200 mg	7.5 mg
5	4.5 mg	250 mg	10.0 mg
6	6.0 mg	300 mg	12.5 mg
7	7.5 mg	400 mg	15.0 mg
8	9.0 mg	500 mg	17.5 mg
9	12.0 mg	600 mg	20.0 mg
10	15.0 mg	800 mg	25.0 mg
11	18.0 mg	1000 mg	30.0 mg
12	21.0 mg	1200 mg	33.3 mg
13	24.0 mg	1200 mg	33.3 mg

4.2 Summary of Ropinirole's Pharmacokinetics

Ropinirole's Tmax after a single oral tablet was 1.4 hours with a mean terminal elimination half life of about 3 hours. Ropinirole undergoes extensive hepatic metabolism with 5% to 10% of the dose eliminated unchanged in the urine. According to SKB, ropinirole is not an inhibitor of the P450 system. Increases in Cmax and AUC were proportional with dose over the range 0.25 to 2.5 mg. Ropinirole binds to plasma protein to a limited extent (10 to 39%), and food decreased the rate of ropinirole absorption at steady state both in PD patients and healthy volunteers.

4.3 Description of the ISS Population

In the phase 2/3 studies included in the ISS, there were 1364 PD patients who were exposed to ropinirole. Of these, 515 and 849 were observed in ET and AT studies with 157 ET and 298 AT patients observed in placebo controlled studies. Of the 157 ropinirole ET patients, most (116) were from US study 054.

The demographic characteristics of the combined ET and AT population were generally

representative of the expected demographics of PD patients. The mean age varied across the treatment groups from 62-65, with 8%-12% of all patients >75 years of age. Approximately 60% of the populations were male and greater than 90% were Caucasian.

There was little difference in age between ET and AT patients across the ISS. In study 054, the mean age was 62.0 (SD; 10.6, Range; 33- 84) while in study 044, the mean age was 63.4 (SD; 9.4, Range; 42-85). AT patients had a longer duration of PD at baseline than that in ET patients; 7 years compared to 2 years. Not surprisingly, AT patients had received l-dopa therapy for about 7 years and were mostly rated in Hoehn and Yahr Stage II or III at baseline while ET patients could not have received l-dopa therapy longer than 6 weeks and most were rated as Hoehn and Yahr Stage I or II. ET patients were also less likely to have a history of hallucinations at baseline, 1% compared to about 5% of AT patients.

Concomitant use of antiparkinsonian medications also varied between AT and ET patients and by study. As with l-dopa therapy, AT patients were not restricted in the extent of prior use of other dopaminergic therapy. However, both ET and AT patients were could use selegiline during study with no restriction on the extent of its prior use at baseline. In the ET studies that had an active comparison group (053 and 056), continued use of amantadine and anticholinergic therapy was also allowed but their dosage could not change. In the US study 054 (ET patients), "rescue" therapy with Sinemet was allowed, but exactly how this was applied was left up to each investigator.

Across the ISS, there was little difference in demographics or PD history by presence of selegiline use at baseline. However, in study 054, there were fewer users of selegiline that were rated in higher Hoehn & Yahr stages and selegiline users had a longer duration of PD disease (28.9 months) compared to the nonusers (18.5 months).

Given that patients taking most CV medications were excluded from US studies 054 and 044, one would have expected less underlying CVD in US studies. Unfortunately, disease co-morbidity prevalence was not compared in the ISS. Based upon data in the study reports for 054 and 044, about 15% of patients had baseline hypertension and 23% of patients were on a non-excluded CV medication at baseline which was typically a diuretic. Given the age of the patients in these 2 studies, the prevalence of CVD seems several fold less than that expected in the general US population of comparable age.

4.4 Review of Sponsor's AE Surveillance, Coding of AEs and Approach to Evaluating the Safety of Ropinirole.

According to SKB, surveillance for AEs occurred at each study visit in all studies. A treatment emergent AE was defined as any event or disease which was not present at

baseline, or which if present increased in frequency or severity while in study irrespective of any belief by the investigator regarding causality. Surveillance focused on all events whether asymptomatic changes in laboratory findings including exacerbation of pre-existing conditions or events such as PD, intercurrent illnesses, and drug interactions.

Because of the ropinirole's dopamine agonist activity and because it caused hypotension and orthostatic hypotension in animals, supine and standing BPs were collected across phase 1, 2, and 3 studies. Patients were checked for postural changes by comparing 5 minute supine BPs with 2 minute standing BPs (after being supine not sitting). While the method of BP measurement was standardized across studies, the timing of BP measurement with respect to last study drug dose was not standardized. For example, in the phase 1 studies and study 032 (non-US placebo controlled study in ET patients), supine and standing BP were measured at specific time points following study drug while in study 054, recorded supine and standing BPs were measured unrelated to the timing of study drug.

In coding the AEs, SKB used the WHOART dictionary. Because certain investigator verbatims were judged to be related to an event of particular interest, some specific coding rules were applied. The investigator verbatims "freezing", "rigidity", "blocking", "off", "shuffling", "shuffling gait", and "stiffness" (except when referring to joints) were coded with the WHOART term "worsening of Parkinson's disease". The investigator verbatims "abnormal involuntary movements", "jerks of limbs" and "twitching" were coded with the WHOART "dyskinesia". The investigator verbatims "dizziness", "hypotension" and "vertigo" were coded with the WHOART "orthostatic hypotension" when noted to be postural in character. The investigator verbatims for "falls" that were mentioned without patient injury were coded with "postural instability". The investigator verbatims of "unintentional" or "accidental overdose" were coded as "drug level increased".

In reviewing the NDA, it appears that the approach described by SKB to ascertaining and describing treatment emergent AEs was generally followed in most studies including studies 054 and 044. Studies 054 and 044 also required a patient visit after study drug was discontinued with the visit occurring between 4 and 14 days after the last dose. In study 054, 12 lead electrocardiograms (ECGs) were performed at screening, 3 and 6 months. ECGs were available for review for 221 patients of the 241 patients who participated in this study.

In addition to having the investigator code AEs as to degree of medical severity, SKB identified AEs meeting the regulatory definition of serious. However, it appears that in the ISS sections that discuss serious AEs, AEs have been included that were also judged to be medically serious irrespective of whether the regulatory definition of serious was appropriate.

On confusing aspect of the ISS was the definition of concurrent illnesses and whether such events should have been considered treatment emergent AEs. Although not well described, it appears that diseases incident during study such as depression, anxiety, IHD or hypertension were classified as concurrent illnesses and not as treatment emergent AEs. While a separate discussion of concurrent illnesses was provided, their definition may have included diseases that were also present at baseline making it difficult to identify specific diseases diagnosed during study. SKB Tables 5.7 and 5.8 from the ISS summarize concurrent illnesses for ET and AT patients respectively.

The NDA summarized deaths, serious AEs, and overall drop outs from completed and ongoing studies using a cutoff date of 5/31/95 while other AEs were summarized using a cutoff date of 10/01/94. Patients had a unique identifier and most patients were counted only once except where placebo patients entered a ropinirole extension (24 patients), and where patients entered multiple extension programs (8 patients). Eight patients were excluded from the ISS because they were randomized to ropinirole but did not receive it or their center was excluded because of concerns regarding "good clinical practices" (n=4). Summaries of the experience of the last 4 patients were appended to the NDA and were available for review.

In the ISS, SKB described common AE occurrence by focusing on AEs likely to be causally related to ropinirole. Potential causality was defined as a greater than 5% increase in the risk compared to placebo or active comparison group. Because of this definition, the relative magnitude of AE occurrence could have been as much as 5 times greater with ropinirole (ie; 5% in ropinirole compared to 1% in placebo) and this AE would not have been included in the discussion. Using this definition of causality, a dose response analysis was provided both for predicted plasma concentration and dose level at the time of the event. Since dose escalation was used in all clinical studies, a dose response analysis could have been confounded by time since first exposure. In addition, SKB counted some patients more than once in this analysis. Patients that had an increase in clinical severity (mild, moderate and severe) at different doses could have been counted as many as three times, but such patients were counted once within a corresponding dose. AE occurrence was also described by time since first exposure. In this analysis, patients were counted only once with the date of first occurrence used to calculate time.

To evaluate potential modification of risk attributable to ropinirole by concurrent medications, underlying diseases or in demographic subgroups, SKB focused such description on AEs with an absolute risk of at least 5%. Concurrent medications or concurrent diseases were selected for study if they had a prevalence of 10% in the study population (ET and AT combined). The following concurrent medications were selected: selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricylic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and tocopherol. The following

concurrent diseases were selected: anxiety, conduction disorders, constipation, depression diabetes, hypertension, insomnia, ischemic heart disease (IHD).

To identify potential modification in the risk attributable to ropinirole, SKB listed the absolute AE risks in ropinirole patients with the characteristic of interest and implicitly compared it to ropinirole patients without that characteristic. Any differences were then also implicitly compared to that across the same characteristic for comparison groups. This approach effectively addresses the attributable risk, but makes it difficult to review since neither attributable or RRs have been calculated. Focusing on the absolute risk differences between ropinirole patients with a characteristic compared to those without it does not speak to modification since the same degree of effect could be occurring within placebo patients. Thus, review of the tables provided by SKB required calculation of the RRs to consider SKB conclusions about risk modification and was limited to characteristics that had significant prevalence in the placebo group. In addition to gender and age, potential modification in ropinirole risk was reviewed for seligiline use, HCTZ use and hypertension.

SKB Table 13.7 shows the hematology and chemistry laboratory parameter increases that were defined as values of potential concern. SKB identified patients with laboratory parameters with consecutive values at or above the value of potential clinical concern (F3 flag), and all patients with a single extreme value (F4 flag). For hepatic enzymes, clinical concern was set at 2.5 times the ULN and extreme values were defined as 4 times the ULN. All study protocols required at least baseline and ending lab with some studies requiring more frequent blood collection. In the ISS, clinical summaries were provided for patients with at least 2 extreme values or for patients with serious AEs associated with a laboratory abnormality. A complete listing of patients who dropped out associated with any laboratory abnormality was not provided so it was not possible to characterize patient follow-up after any particular abnormality.

4.5 Audit Findings and Specificity of the AE Coding.

The investigator verbatims listed in the CRFs of the 40 deaths and from a sample of AE withdrawals and serious AEs were congruent with those in the data tabulations and described in the narrative summaries. Conversely, the narrative summaries, while providing more clinical detail particularly about past medical history, described AEs that were generally identified in the CRF.

In general, the WHOART coding of the investigator verbatims seemed reasonable except for a few instances. Because of the coding rules that were described in section 4.4, the specificity off "orthostatic hypotension" was also likely reduced. The protocol definition of orthostatic hypotension for all studies in the ISS was defined as a decrease in systolic BP of 20 mm and/or a decrease in diastolic of 10 mm Hg, irrespective of

presence of symptoms.[4] However, in the ISS, the WHOART code "orthostatic hypotension" also was used to code postural symptoms (dizziness on standing) with or without objective change in BP. This approach appears to have been applied because several patients, particularly in the phase 1 studies, could not have their standing BPs measured because of orthostatic symptoms and in some cases, syncope. Apparently because such patients would not have be coded as having orthostatic hypotension, SKB broadened its definition. While this approach may increase the sensitivity of the code to identify clinically significant events, its specificity most likely has been reduced (increasing false positives) biasing any difference between ropinirole and a comparison group towards the null. Of course, the sensitivity of the code probably varied across studies anyway since BP was measured irrespective of the timing of dose for some studies.[5]

Other WHOART codes may also have been applied in a non-specific way. Several reports of falls associated with use of ropinirole have been coded as "postural instability" and several unintentional or accidental overdoses have been coded as "drug level increased".

In addition to a general check of the validity of data submitted in the NDA, the supine and standing BPs that were recorded for studies 054 and 044 were also reviewed. This review focused on obvious inconsistencies and biases and didn't use formal sampling to statistically test for potential bias. While the "even digit" bias that is seen with in BP data was obvious, there also seemed to more "0s" recorded as the last digit than one would expect suggesting that the BPs were rounded off by tens. At 1 site, standing BPs were exactly the same as supine BPs for all patients entered by that site.

4.6 Extent of Exposure

4.6.1 Extent of Exposure, Overall and Stratified by Duration of Use

Table 3 shows the number of patients and person-time of use both overall and by duration of use. Person-time was estimated from SKB's tables showing the number of patients observed by 3 month intervals. Overall, there were 1364 ropinirole patients

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[4] We will use this definition to reflect objective orthostatic hypotension in subsequent discussion.

[5] The effect of such misclassification and differential ascertainment by study would limit the full database's ability to observe any true difference in orthostatic hypotension between ropinirole and a comparison. Thus, SKB's noting in the proposed labeling that there was no difference in orthostatic hypotension between ropinirole and placebo probably has no valid basis.

observed in phase 2/3 studies with about 1165 PYs of ropinirole use, with more than 500 PYs of use in both ET and AT patients. Slightly more than 100 PYs of ropinirole use occurred after the first 12 months of use in both ET and AT patients.

Table 3. Number of Patients and Estimated Person-Years in Patients with ropinirole Use up to 2 Years		
	N	Person-Years**
Phase 1		
Healthy Volunteers	110*	
PD Patients	47	
Phase 2/3		
All Patients		
0-24 Months	1364	1165
>6-24 Months	972	601
>12-24 Months	599	212
ET Patients		
0-24 Months	515	514
>6-24 Months	416	283
>12-24 Months	267	112
AT Patients		
0-24 Months	849	651
>6-24 Months	556	319
>12-24 Months	332	100

*7 patients in counted twice - in two different studies. Not clear whether there are 110 or 111 healthy volunteers.

** 33 ropinirole patients continued use beyond 24 months. This person time was not estimated. PYs added for ET and AT patients may not equal the total because of rounding.

4.6.2 Extent of Exposure by Dose

Based upon SKB's description of exposure by dose, 176 of the 1364 patients in phase

2/3 studies achieved the highest dose of 24 mg/day, 79 ET and 97 AT patients. Of the 176 patients that reached 24 mg/day, 124 were exposed to this dose for more than 12 weeks.

SKB Tables 4.4a and 4.4b show the mean dose separately in both ET and AT patients. Overall, about 7% of patients averaged more than 18 mg per day for the time they were observed in study.

In addition to mean daily dose, the extent of use was described using several other statistical summary measures including dose of longest duration, maximum dose, dose at study endpoint, etc. However, all these measures summarized the total person time of use for each patient according to that summary measure. A patient spending 1 day at a maximum dose would have all person-time summarized based upon that dose for that one day.

4.6.3 Extent of Dosing in Selected Demographic Groups

In both ET and AT patients, ropinirole daily dose tended to decrease with increasing age and in females. There were too few non-white patients to generalize about any dosing differences by race. Dose was not described as a function of concurrent medications or by baseline co-morbidity.

4.7 Phase 1 Safety

In the phase 1 studies included in the ISS, ropinirole was administered to 110 young (mean age 29.7 years, range 19-49 years) healthy male volunteers in 11 single dose studies that had multiple dose sessions. Eight of these included oral dosing sessions. The exact number of volunteers exposed isn't consistently described in the ISS or in the NDA clinical pharmacology section. In several places in the NDA, 111 volunteers are mentioned as participating in phase 1 studies and as many as 7 healthy volunteers may have been counted at least twice after participating in several single dose studies.

Of the 110 healthy volunteers, 70 were exposed to oral ropinirole, 18 exposed to oral and IV, and 22 exposed to ropinirole by only the IV route. In healthy volunteers, there were 302 ropinirole dosing sessions at doses ranging from 0.01 mg to 2.5 mg and 63 placebo sessions. In addition to healthy volunteers, 47 PD patient volunteers were exposed to ropinirole in phase 1 studies with 13 exposed to ropinirole in single oral doses up to 12 mg ropinirole and 34 receiving repeat oral doses of ropinirole up to 2 mg (some were counted in both groups, and counts were also not clearly presented in the NDA). Apparently, there were no placebo dosing sessions in patient volunteers.

According to SKB, ropinirole was well tolerated at doses up to 1 mg in healthy and patient volunteers. At higher doses, both groups developed nausea and orthostasis

except when ropinirole was co-administered with domperidone, a peripheral D2 blocker. Tables 7.5 and 7h from the ISS and included in the appendix, summarize the AEs observed in healthy and patient volunteers. In healthy volunteers, nausea, dizziness and orthostatic hypotension were significantly greater with ropinirole than with placebo whereas nausea dizziness and headache were the most common AEs reported in patient volunteers (no placebo exposure in patient volunteers).

Across the phase 1 studies, no deaths were reported. Four patients and 1 heathy volunteer had AEs that were classified as medically serious. Patient 003.001.00001 was a healthy volunteer who had a cardiac arrest 1 hour after a 1 mg dose. The AE began as he was standing for a BP measurement. Two minutes after standing, his BP decreased from 120/70 to 92/66 (pulse rate 81). He was immediately placed supine and within seconds developed bradycardia that was followed by loss of consciousness (LOC) and 26 seconds of asystole. Normal sinus rhythm returned without any medical intervention followed by a rapid recovery of hemodynamic status (blood pressure 117/56 and pulse rate 43 within three minutes of the onset of symptoms). His recovery was associated with sweating, pallor, nausea and a brief period of vomiting. He was able to stand uneventfully after four hours and subsequent medical evaluation was negative. There was no evidence of QT prolongation or ventricular dysrhythmia reported during the continuous ECG monitoring of this event.

Patient 007.001.00002 was a 66 Y/O female patient volunteer who had nausea and orthostatic hypotension after a oral 0.8 mg dose which was her fourth dose of the study. Pre-dose BP was 110/72 and 2 hours after the dose the standing BP was not recordable. After being placed supine, her BP was 94/60 with a pulse of 64. No treatment was given and she was withdrawn from study. There was no mention of a prior underlying CVD.

Patient 019.001.00004 was a 51 Y/O male patient volunteer also in a dose escalation study. He had been in study about 4 days and was on 0.8 mg TID. He complaining of being tired with excessive perspiration and was withdrawn. No BP changes were mentioned and no follow-up was given.

Patient 027.001.00009 was a 68 Y/O patient volunteer who had hypertension at baseline. After her first dose of 0.2 mg, her BP increased to 190/115 and was associated with a headache. It was treated with sublingual nifedipine. Patient 021.001.00006 was a 61 Y/O female who also developed an increased BP after her first dose. Four fours after a 1 mg dose her BP was 200/110 and was not associated with any symptoms. It resolved without treatment.

In patient volunteers, the AE dropout risk was 25.5% (12/47) with the most common AEs associated with dropout being nausea, dizziness, vertigo and hypotension. No discussion was provided in the ISS of dose at dropout. Two healthy volunteers dropped

out of study who had received ropinirole, 1 associated with general GI symptoms and the other following increased liver enzymes that were observed 1 day after a single oral dose.

As expected, ropinirole was shown to decrease standing BP in healthy volunteers. Both 1 hour post-dose systolic and diastolic standing BPs declined at doses as low as 0.25 mg with statistically significant differences from placebo observed in 1 0.25 mg study. Doses higher than 0.25 mg were always associated with decreases in standing BP that were statistically different from placebo. At 1 mg, the mean decreases in systolic and diastolic BPs 1 hour post-dose were about 15 and 10 mm Hg, respectively. Ropinirole's effect on standing pulse was not as consistent. At 1 hour after a 1 mg dose, the mean decease was about 8 beats per minute (bpm) while after 2 hours, the mean increase was about 15 bpm. Ropinirole did not appear to affect cardiac conduction and had little effect upon supine BP. Whether similar changes in BP was observed in patient volunteers was not well described in the NDA.

There were 9 healthy volunteers who were coded as having orthostatic hypotension all but 1 following oral ropinirole. One placebo patient was also coded as having orthostatic hypotension 8 hours post dose. Of the 8 healthy volunteers with an event occurring after oral ropinirole, 6 had objective evidence of orthostatic hypotension and 2 others were too symptomatic to stand for a BP (these 2 were dosed at 1 mg). Seven of the 8 events following oral dosing and the 1 event after IV were associated with decreased heart rates. Of the 5 with objective orthostatic hypotension, 2 were observed about 50 minutes after a 1.25 mg oral dose and 1 was associated with syncope and cardiac arrest 1 hour after a 1 mg dose (discussed above). One objective case of orthostatic hypotension was observed 6 hours after a 1.25 mg dose. In the Japanese phase 1 study which had 29 healthy volunteers, orthostasis was also reported at single doses as low as 0.4 mg although it was not clear whether this meant objective BP changes or significant postural symptoms without BP changes or both.

Ropinirole also increased the resting supine heart rate in healthy volunteers. At 0.64 mg, the mean increase in heart rate was about 5 beats per minute (bpm) while at a 1 mg dose, the mean increase was about 10 bpm, but highly variable between studies. Differences with placebo were statistically significant at doses of 0.64 mg and above. No clinical events appeared to be associated with the increase, and in patients that had an increase in heart rate, there was no change in supine BP. SKB considers this increase to be small and not likely to be of clinical relevance.

Other ropinirole effects observed were as follows: 1) decreased serum prolactin occurring in single doses ranging from 0.2 to 0.8 mg and 2) decreased urinary uric acid secretion.

4.8 Mortality in Phase 2/3 Studies

4.8.1 Ropinirole Mortality Compared to Placebo and Bromocriptine

Through May 31, 1995, there were 40 deaths observed in the development program, of which, 32 occurred or the event leading to death began within 30 days of the last dose of ropinirole, placebo or bromocriptine. There were no deaths observed with l-dopamine although there was limited person-time of use. Of the 32 deaths, 15 occurred with ropinirole and of the 32, 18 occurred in the AT studies, 13 in the ET studies and 1 was a sudden ropinirole death in a PK interaction study. There were no ropinirole deaths within 30 days of last use in either study 054 or 044.

Two non-US studies accounted for 16 of the 32 deaths. Study 043 was a 6 month randomized comparison of ropinirole and bromocriptine in AT patients while study 053 was a similar comparison in ET patients. In both studies there was a similar dropout hazard by study week between treatment groups. In 043 the 6-month mortality risk was 1.4 per 100 patients (5/367) for ropinirole and 2.1 (4/188) for bromocriptine. In 053, the 6-month mortality risk was 0.6 per 100 patients (1/168) for ropinirole and 3.4 (6/167) for bromocriptine.[6]

Table 4 shows the estimated mortality rates for ropinirole placebo and bromocriptine separately in ET and AT patients. PYs of use have been estimated from the 3 month patient participation tables provided by SKB. In either ET or AT patients, ropinirole mortality was less than that observed with placebo or bromocriptine. This decrease was statistically significant in ET patients when ropinirole was compared to bromocriptine.

While ropinirole mortality was about 2 fold greater in AT compared to ET patients, a similar difference between AT and ET patients was not observed for placebo or bromocriptine. In a recent publication[7] describing mortality of the Honolulu Heart Study cohort, the mortality rate in 65-69 year olds who developed PD was about 5 per 100 PYs (8 deaths) or slightly greater than that observed with bromocriptine.

Table 4. Rate of Mortality Observed in Ropinirole Development Program

	Deaths*	PYs	Rate / 1000 PYs	RR**; 95% CIs

[6] p=.07 by Fisher's exact

[7] Morens DM. Evidence against the operation of selective mortality in explaining the association between cigarette smoking and reduced occurrence of idiopathic parkinson disease. Am J Epidemio 1996; 144:400-404.

ET Patients				
Ropinirole	4	514	7.8	
Placebo	3	106	28.6	0.28; 0.05,1.88
Bromocriptine	6	174	34.5	0.22; 0.5,0.95
AT Patients				
Ropinirole	11	651	16.9	
Placebo	2	77	26.0	0.65; 0.14,6.04
Bromocriptine	5	157	31.8	0.53; 0.17,1.95

*1 patient was not included that was in a PK study.
** Rate Ratio for Ropinirole

4.8.2 Description of Deaths Observed During Ropinirole's Use

Of the 15 ropinirole deaths, 12 were potentially CV in nature. These 12 deaths are summarized below.

Patient 00052 was a 71 YO male who entered the AT study 036 and then entered its extension 037. His baseline history was mostly negative, but he did have a baseline chest x-ray interpreted as showing an enlarged heart. The baseline ECG was read as showing a left ventricular strain pattern with some left axis deviation. During the study he was increased to a 6 mg per day and was on this dose for about 4 months before his death. There was no reports of syncope or any complaints of chest pain. At about the same time his ropinirole dose was increased to 6 mg he was diagnosed with hypertension and started on HCTZ without K^+ supplementation. On day 266 he died at home. The cause of death was reported as an MI although there was no evidence substantiating an MI and there was no mention of any autopsy findings.

Patient 00020 was a 78 Y/O male who was in the AT studies 040/041. The patient entered the 041 extension after completing 040 at 6 mg per day. In 041, he was escalated from 1.5 mg per day. to 12 mg per day without difficulty. He was stable on this dose for about 3 months when he reported dizziness. The dose was decreased to 9 mg per day, and then 6 mg per day after he reported GI upset and continued dizziness. Because of increasing tremors, the daily dose was increased to 7.5 mg. where it remained until his death about 3 months latter. One day before his death, he was treated with Biaxin for a URI which was followed 1 day latter by hospitalization for hematemesis and moderately severe diffuse abdominal pain. He had several episodes of emesis and a subsequent respiratory arrest. He died several days thereafter. No autopsy was performed.

Patient 01369 was an 88 Y/O female who was in the AT study 043 and was dose escalated to 18 mg per day without difficulty. After 23 days at this dose, the patient developed severe CHF and died 2 weeks latter. No information was provided regarding the event and no autopsy was performed. The patient had an extensive baseline history including IHD, hypothyroidism, diabetes, and abnormal repolarization. Medications at baseline included lasix and nitrates.

Patient 01081 was 54 Y/O male who was also in 043. After 5 days at 13.5 mg per day he was found dead in his room. No autopsy was performed. Baseline history was unremarkable. No concomitant CV medications were given during the study. About 2 weeks before death, the patient was coded as having orthostatic hypotension.

Patient 01225 was a 79 Y/O male also in 043. Patient was titrated to 9 mg per day without difficulty. Two days after this, he developed chest pain with peripheral edema and was treated for CHF with lasix. About 2 weeks latter his daily dose was increased to 12 mg and about 2 weeks after this, he developed chest pain which was relived with nitroglycerin. He died suddenly 2 days latter and no autopsy was performed. Baseline history was significant for CHF and hypertension. Nitrates were used at baseline.

Patient 00504 was a 66 Y/O female also in 043. Following her placebo run-in period she started ropinirole at 1.5 mg per day. Apparently, she discontinued ropinirole after 1 day for undefined reasons. One week latter she had a respiratory arrest. What happened, if anything, in this week was not described. Her baseline was negative for CVD and she was taking no CV medications.

Patient 00772 was a 80 Y/O male enrolled in the ET study 053. She was doing well in the study at a daily dose of 10 mg per day. She was on this dose for several months when she was found comatose and hospitalized. She died 1 week latter and there was no autopsy. The cause of death was stated as a CVA, but there was no confirming evidence presented. There was no baseline history of CVD.

Patient 00058 was a 70 Y/O male enrolled in the ET study 058. Three days after reaching 9 mg per day, he had a witnessed sudden death. The cause of death was reported as an acute MI, but no supporting evidence was provided and there was no autopsy. His CRF could not be located for review. According to the narrative summary, he didn't have a baseline history of CVD. According to his wife, he was complaining of chest pain that began about 2 weeks prior to his death.

Patient 03010 was a 75 Y/O female who completed the AT study 023 and was enrolled in the compassionate use study 090. She was doing well up until she was found death at home. No cause was reported and there was no autopsy. Her baseline history was negative for CVD and she was on no CV medications. Her course in the studies was uneventful except for hematochezia.

Patient 00051 was a 75 Y/O male who completed the AT study 036 and was enrolled in the compassionate use study 090. He was doing well in 090 for about 1 year when he had a sudden death that was called an MI. At baseline he was noted as having IHD, but was not taking any CV medications. During 036 he was diagnosed as having angina and was started on nitrates with improvement in chest pain. No autopsy was performed.

Patient 01630 was a 70 Y/O male who competed the AT study 043 and entered the compassionate use study 090. He was doing well at 9 mg per day for about 2 months in 090 when he was dose reduced to 3 mg per day shortly before he had angioplasty for unstable angina. His post-surgical follow-up was complicated by a CVA with left sided hemiplegia. He died after developing aspiration pneumonia and septic shock. At baseline he was noted to have IHD with prior coronary bypass. The reason for the dose reduction was not discussed nor were any AEs noted on the CRF at the time of the dose reduction.

Patient 00043 was a 66 Y/O female participating in the PK study 092. This study was examining ropinirole kinetics at multiple dosing steady states. Three days after reaching 12 mg per day she had a witnessed syncopal episode at church which was described as a LOC with a fall. While there was no significant injury, she was hospitalized for observation during which ropinirole was discontinued. Ropinirole was resumed upon discharge 2 days latter and she was titrated to 16.5 mg daily. About 1 week after reaching 16.5 mg she fell and bruised her calf muscle. This event was not well described in the CRF. Shortly thereafter she was diagnosed with a DVT and hospitalized for treatment with heparin. She continued in the study and was titrated up to 18 mg. Four days after reaching this dose she died in her sleep. No autopsy was performed. She had non-insulin dependent diabetes at baseline.

4.9 All-Cause and AE Dropout Risks

4.9.1 ET Studies

SKB table 6.4 shows the reasons for study dropout in ET patients by treatment group. Using a data cutoff date of 5/31/95, the all-cause dropout risk was 27% (140/ 515) in ropinirole ET patients compared to 23% (34/147) in placebo, 16.9% (15/89) with L-Dopa and 28.5% (37/167) with bromocriptine. As of this date, 281 ropinirole patients and 18 placebo patients were still in study, and no patients had completed with either L-Dopa or bromocriptine.

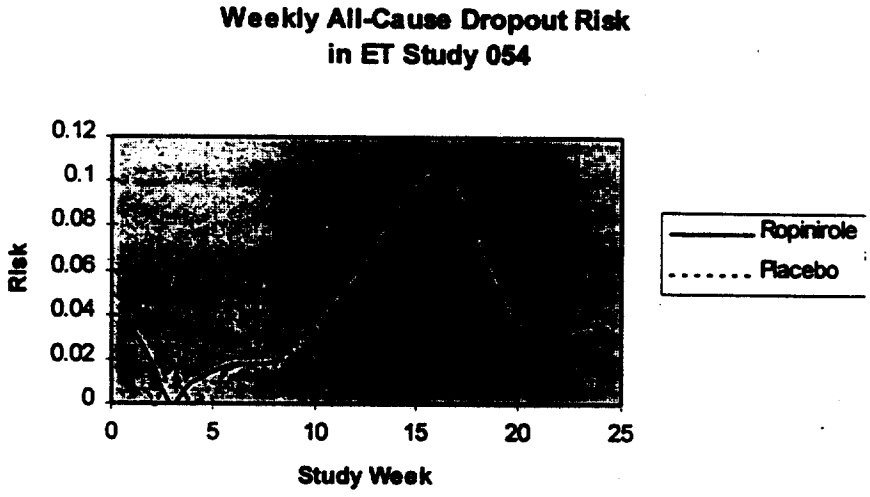
There were differences in reasons for dropout by treatment group. The AE dropout risk was 17.1% with ropinirole (88 patients) compared to 10% with placebo (14 patients), but was similar to that seen with L-Dopa and bromocriptine. A larger percentage of patients was withdrawn from study because of protocol deviations with ropinirole than other treatment groups, and both ropinirole and bromocriptine had about 2% of patients

that were lost to follow-up.

SKB table 6.1 shows that the all-cause dropout risk and AE dropout risk associated with ropinirole use were variable across ET studies. In study 053, a comparison between ropinirole and bromocriptine and the largest non-US ET study (ongoing as of the cutoff date), the ropinirole group had an all-cause dropout risk of 25% and an AE dropout risk of 12.5%.

In study 054, the all-cause dropout risk was almost 2 times greater with ropinirole, 31.9% (37/116) compared to 16.0% (20/125) with placebo. This difference was mostly due to a difference in dropouts associated with AEs. In ropinirole treated patients, the AE dropout risk was 23.3% (27/116) compared to 10.4% with placebo (13/125).[8] The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

Using data provided in the 054 study report, the following figure shows the all-cause dropout risk by week of study. The increased risk of dropout observed with ropinirole use is mostly attributable to differences with placebo that occurred from 10 to 20 weeks after study entry. While such a divergence in risk with time suggests a temporal factor such as dose, neither the individual study report nor the ISS provided data on daily dose at time of dropout. Since patients continuing in study had to be increased to at least dose level 5 (4.5 mg per day) and this level would have achieved prior to 10 weeks in most patients, the daily dose at 10-20 weeks was probably at or above 4.5 mg per day.



[8] p=.009 for the difference in risk by Fisher's Exact

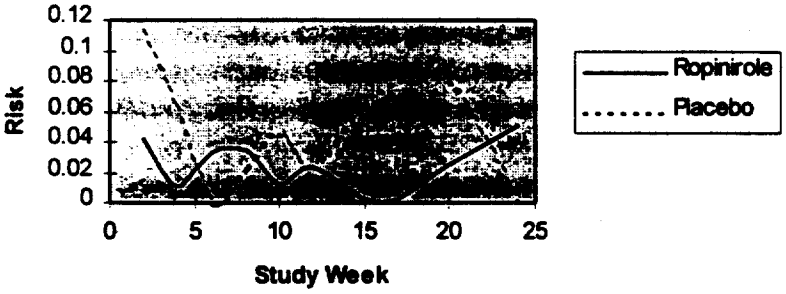
4.9.2 AT Studies

SKB's table 6.5 shows the number of dropouts by study as well as the reasons for dropout in AT patients. The all-cause dropout risk was 29.3% (249/849) with ropinirole compared to 39.1% in placebo patients (59/151) and 22.3% in bromocriptine (42/188). As of the cut off date, 207 ropinirole patients and 30 placebo patients and 58 bromocriptine patients were still in study.

The AE dropout risks for ropinirole, placebo, bromocriptine were 17.3% (147/849), 15.9% (24/151) and 15.4% (29/188), respectively. The percentage of placebo patients dropping due to lack of effect was higher than in other treatment groups and accounted for the increase in all-cause dropout with placebo. Ropinirole had a slightly higher percentage of lost to follow-up (0.9%) than placebo but lower than with bromocriptine (1.6%).

In study 044, the all-cause dropout risk with ropinirole was 22.1% (21/95) compared to 35.2% with placebo (19/54). The AE dropout risk with ropinirole was 15.8% (15/95) compared to 16.7% with placebo (9/54). The following figure shows the dropout risk by week of study. It is essentially the reverse of the risk seen in 054 with placebo having the highest risk from 10 to 20 weeks. As was observed across all AT studies, the increase in all-cause dropout risk in placebo was due to dropouts due to lack of effect.

Weekly All-Cause Dropout Risk in AT Study 044



4.10 Clinical Characteristics of AEs that were Associated with Dropout

Across all phase 2/3 studies, 71 ropinirole patients dropped out of study associated with a serious AE occurrence, 26 ET patients and 45 AT patients. SKB table 8.4 provides a listing of all serious AEs associated with dropout across all ropinirole studies by patient. These events were generally reviewed using the narrative summaries and other supporting data. Overall, there were no cases of agranulocytosis, aplastic anemia, serious skin reactions such as Steven's Johnson Syndrome, hepatic failure or necrosis, renal failure or worsening of renal function or rhabdomyolysis that were associated with dropout. One patient was discontinued for "immune thrombocytopenia" and will be discussed in 4.11 along with other serious hematologic AEs.

4.10.1 Clinical Characteristics of AE Dropouts in ET Patients

4.10.1.1 Serious AEs Associated with Dropout in ET Patients

The serious AE dropout risk in ET patients using ropinirole was 5.0% (26/515) compared to 5.4% with placebo (8/147). A larger proportion of patients on placebo were classified as having a serious AE that was associated with dropout (8 of 14 compared to 26 of 88 with ropinirole). This differential classification explains why there was no difference in serious AE dropout risk between ropinirole and placebo, but all-cause AE dropout risk was greater with ropinirole. In study 054, the serious AE dropout risk was 6.9% with ropinirole (8/116) compared to 3.2% (4/125) in placebo with little difference in the proportion of AEs associated with dropout that were classified as serious.

Based upon a review the investigator verbatims of the 26 patients with serious AEs associated with ropinirole dropout in ET patients (Table 8.4), 8 had AE that were cardiovascular in nature (Table 5) with 5 of the 8 were enrolled in study 054. The events occurring in these 8 patients are summarized below.

Patients 054.019.00125 and 054.002.00186 also had syncopal events associated with the event listed in Table 8.4. Patient 054.002.00186 was a 74 Y/O male who was titrated to 24 mg per day without problems. Two weeks after achieving that dose he had syncope and was hospitalized with ropinirole discontinued at hospitalization. He was diagnosed with sick sinus syndrome and 1 day after hospitalization he had a permanent pacemaker inserted. He had a history of syncope and collapse at baseline, but no history of CVD and was not taking any CV medications at baseline or during study.

Patient 054.019.00125 was a 63 Y/O male who was titrated to 9 mg per day without difficulty. About 3 weeks after achieving that dose, he experienced syncope which was shortly followed by 2 more episodes and hospitalization with discontinuation of ropinirole. No data was provided on his workup or treatment. His baseline history was

significant for IHD with previous bypass grafting.

Patient 053.026.00909 was a 68 Y/O male who was titrated to 4.5 mg per day without difficulty. Five months latter he was admitted to an ICU with a documented MI. The hospital course was complicated by bradycardia and hypotension.

Patient 053.035.01030 was a 68 Y/O female who had 2 episodes of orthostatic hypotension at 3 mg per day with the last episode managed in the hospital. Ropinirole was discontinued at hospitalization and she was discharged without treatment. No BP data was provided. She had a history of hypertension at baseline.

Patient 053.043.00193 was a 67 Y/O male hospitalized for ventricular tachycardia and bradycardia (< 40 beats/min) two days after reaching 9.5 mg per day. He had a history of IHD and was treated for such at baseline. In the weeks before the event while in study, he was examined twice by a cardiologist for PVCs. The clinical nature of the events leading up to the hospitalization was not well described by any of the available data.

Patient 054.004.00146 was a 60 Y/O male who had chest pain, bradycardia and PVCs 6 days after reaching 21 mg per day. Apparently, this event was not treated or worked up. Ropinirole was continued until 1 month latter when it was withdrawn, but without a clear reason. Whether ropinirole as withdrawn abruptly or tapered was also not described. Three days after ropinirole withdrawal, he again had chest pain causing him to go to the ED and was hospitalized for a work-up. While findings from this evaluation were not discussed, there was no treatment on discharge.

Patient 054.009.00051 was a 60 Y/O female with a baseline history of SVT which recurred 1 day after reaching 18 mg per day. Over the next several months, she had several more episodes of SVT that were self limited with 1 episode observed by her internist. She was tapered to 9 mg per day. Several hours after a routine study visit she was hospitalized after having a symptomatic CV event. This was described in the narrative summary as a "wandering pacemaker". Ropinirole was discontinued at hospitalization and there was apparently no intervention in the hospital. Through 5 months of follow-up after the hospitalization, there were no more reported SVT episodes.

Patient 054.017.00216 was a 75 Y/O male with a history of atrial fibrillation at baseline. He was discontinued at 0.75 mg per day after having an episode of atrial fibrillation.

As mentioned earlier, there were 8 patients in study 054 that dropped out associated with serious AE occurrence with 5 of these summarized above. The three remaining patients had a generalized seizure associated with a meningioma, hospitalization for

headache and vertigo, and hospitalization for thrombophlebitis.

Table 5. Summary of ET Patients with a CV AE and Dropout		
PID	Day of Dropout	Investigator Verbatim
053.026.00909	175	Bradycardia, Hypotension, MI
053.035.01030	41	Orthostasis, Hypotension
053.043.00193	274	Sinus Bradycardia, PVC, V.Tach
054.002.00186	163	Sick Sinus Syndrome
054.004.00146	113	Sinus Bradycardia, Chest pain, Bigeminy
054.009.00051	106	Paroxysmal SVT
054.017.00216	6	Atrial Fibrillation
054.019.00125	113	Sinus Bradycardia

4.10.1.2 Most Common AEs associated with Dropout in ET Patients

SKB table 7.18 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% patients. Nausea, vomiting and hallucinations were associated with dropout in more than 1% of ropinirole patients and occurred 2 times more frequently than with placebo. Three patients dropped out associated with syncope.

SKB Table 24 from the 054 study report (Appendix 2), shows the AEs associated with dropout for study 054. Nausea, dizziness, dyspepsia, bradycardia, palpitations were the most common reasons. Only patient dropped out associated with hallucinations. Based upon our review of all dropouts from study 054, 3 patients who dropped out also had syncope at the time of dropout (2.6%) making syncope the third most common reason. All three of these had been coded as bradycardia. Two of these were classified as serious and have been reviewed in section 4.10.1.1. The other occurred in a male patient with hypertension who withdrew the next day apparently because of concerns raised by his daughter.

4.10.2 Clinical Characteristics of AEs Associated with Dropout in AT Patients

4.10.2.1 Serious AEs Associated with Dropout in AT Patients

Across all AT patients taking ropinirole, the serious AE dropout risk was 5.3% (45/849). In the foreign study 043, which was ongoing as of the cut off date, it was 2.5% with ropinirole (9/367) compared to 2.7% (5/188) with bromocriptine. In study 044, the US AT study, it was 2.1% (2/95) for ropinirole compared to 5.6% with placebo (3/54).

In study 044, the available data for the two patients who dropped out associated with a serious AE were reviewed. Patient 044.003.00088 was hospitalized on day 12 after experiencing choreiform movements, shortness of breath, diaphoresis, chest pains and chest tightness. He was a 66 Y/O male who shortly after reaching 1.5 mg per day had a brief episode of precordial chest pain that radiated to the left shoulder and was associated with dyspnea and SOB. Over the next few days, he had several such episodes and was admitted to the CCU with ropinirole discontinued at hospitalization. There was no evidence of an MI and at discharge he had a negative stress test. His baseline history was negative for CVD and he was apparently very active with no history of exertional chest pain. The investigator diagnosed coronary vasospasm that he attributed to ropinirole. Patient 044.007.00137 was hospitalized on day 159 due to back pain that was secondary to staphylococcus infection of the lumbar disc space.

The investigator verbatims and narrative summaries for the remaining 43 AT patients with a serious AE associated with study dropout were reviewed. While in general the review was not very revealing, there were several episodes of orthostatic hypotension and/or syncope that were associated with ropinirole dropout and classified as serious. These have been summarized below.

Patient 020.001.000006 was a 56 Y/O male who had syncope and bradycardia 1 hour following his first 0.6 mg dose. Shortly following the event, his BP was 110/70 with a pulse of 45. The bradycardia lasted 30 minutes. The event was classified as serious because of investigator concerns, but did not meet the regulatory definition.

Patient 023.003.00002 collapsed 1 hour after a 2.0 mg dose in the investigator's office. He had been on ropinirole for 14 days. The collapse occurred as he was standing for a BP measurement. His systolic BP was 90 with no measurable diastolic. Pulse at this time was 100. No intervention was necessary with the patient having a full recovery. This event was also classified as serious because of investigator concerns, but it did not meet the regulatory definition. His baseline history was negative and he was not taking any CV medications.

Patients 056.024.000575, 057.001.00009 and 099.010.00099 were also study drop outs

associated with syncope. None of the three meet the regulatory definition of serious. Patient 057.001.00009 dropped out after the first dose and patient 099.010.00099 dropped out during dose escalation.

4.10.2.2 Most Common AEs Associated with Dropout in AT Patients

As shown in SKB Table 7.19, the probability of a study dropout that was secondary to nausea, dizziness or hallucinations was about 1% or greater with ropinirole and twice as likely as with placebo.

Table 30 lists the AEs associated with dropout in study 044. (Table 30 lists 19 AE dropouts instead of 15, as stated in section 4.9.2, because 4 patients are included who withdrew because of lack of efficacy as reflected by worsening of PD.) In study 044, there were no AEs that were reported in more than two patients who dropped out.

4.11 Serious AEs Associated with Ropinirole

In the ISS, serious AE risks were not described separately for ET and AT patients. In study 054 (ET patients), the serious AE risk was 19.0% (22/116) with ropinirole and 10.4% in placebo (13/125). Of these 22 patients having serious AEs with ropinirole, 6 were CV in nature. Five of these 6 CV AEs were already discussed as study dropouts. Patient 054.020.00181 was hospitalized for chest pain that was considered non-cardiac shortly after being increased to 12 mg per day. Three days after discharge he had a "pre-syncopal" episode that lasted 10 minutes and was seen in the ED. He was observed for about an hour then discharged. According to the documentation, ropinirole was discontinued that same day because of non-compliance. At baseline, he had a significant history of CVD with prior angioplasty and coronary bypass.

Three of the remaining 16 patients with serious non-CV AEs in study 054, were described under section 4.10.1.1. Of the remaining 13 patients, seven had unintentional overdose, two had surgical treatment of cancer, 1 had surgery for cholecystectomy, 1 was admitted with an embolic event to an extremity, 1 had surgical repair of Peyronie's disease and the other was hospitalized for treatment of DVT.

In study 044 (AT patients), the serious AE risk was 15.8% (15/95) with ropinirole and 24.1% (13/54) in placebo. Of the 15 patients with serious AEs in study 044, 1 was CV in nature. This was the patient diagnosed with coronary vasospasm and summarized in section 4.10.2.1. Of the remaining 14 patients, two patients were also mentioned in section 4.10.2.1, 9 patients had accidental overdoses, 1 patient was hospitalized for urosepsis (whether or not this event was associated with urolithiasis was not noted) and 1 was hospitalized for an orthopedic procedure that resulted from a fall that occurred 16 days after starting ropinirole. The fall was not well described and was not recorded as an AE (044.015.00063).

SKB table 8.1 shows serious AEs that were reported in more than 1% of any treatment group for all patients combined. Careful review of Table 8.1 is necessary since it pools the extension studies with the RCTs resulting in more person-time at risk for ropinirole and a greater opportunity to observe background events. From table 8.1, patients with peripheral ischemia, edema and dyspnea were selected for further review.

The 4 cases of peripheral ischemia appeared to result from baseline peripheral vascular disease and will not be discussed further. There was evidence that edema contributed to these events

Patient 040.008.00089 was typical of several of the patients coded as having a clinically significant peripheral edema. He was a 66 Y/O who had difficulty with peripheral edema throughout the study 041. Several cardiology consults all stated that the cause was non-cardiac. He was eventually discontinued from 041 because of lack of effect.

The patients coded with dyspnea had other ongoing AEs such as CHF or pneumonia. Patient 044.003.00088 who was already summarized had dyspnea with along with the chest pain that was diagnosed as coronary vasospasm.

From SKB Table 8.0 that provides a listing of all serious AEs occurring in ropinirole patients, several patients were selected for further review. Review of patients with serious AEs coded with chest pain or angina did not identify any other patients where the investigator diagnosed coronary vasospasm. However, 1 other patient (056.025.00598) had severe chest patient followed by hospitalization that showed no evidence of an MI. On discharge his stress test was reported as negative, but his clinical history was sketchy with the narrative summary reporting that he had angina at baseline.

Overall, Table 8.0 did not list any patients with serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, seizures or rhabdomyolysis. However, several patients had some AEs that are worth summarizing.

Serious Skin Reactions

Patient 034.008.0092 who was coded with "erysipelas" was not well described by the available data. According to the narrative summary, the event was associated with a "high fever" and the patient was treated with IV antibiotics with hospitalization lasting 2 weeks. There was 1 other patient (053.034.00837) with erysipelas that was hospitalized for 1 week who was also treated with IV penicillin. The data reported for each patient was limited and did not provide a clinical description of the rash.

Seizures

Patient 054.002.00209 who was mentioned under section 4.10.1.1 had an first generalized tonic-clonic seizure followed by a diagnosis of a meningioma made by MRI. There were no other serious AEs that were appeared to be associated with a seizure.

Hematologic Events

Several patients had hematologic AEs that were serious in nature. Patient 036.002.00016 was noted on day 29 to have a decreased H&H and lymphocyte count with an increased BUN. Ropinirole was discontinued and the abnormalities were still present 1 month latter. No further follow-up was provided. Patient 056.007.00148 had a hospitalization for laparotomy that diagnosed metastatic endometrial cancer. Shortly before this surgery, anemia, increased liver enzymes and leukopenia were diagnosed and were considered related to the malignancy. Patient 056.028.00668 had "life threatening" thrombocytopenia that was diagnosed after hematuria and widespread purpura that followed a viral illness. During hospitalization ropinirole was discontinued and he was treated with platelet transfusion, but with no clinical response. No further clinical data or follow-up was provided and apparently a bone marrow was not performed. According to the narrative summary, the etiology was considered to be immune mediated.

GI Hemorrhage

Patient 038.002.00014 had UGI hemorrhage resulting from a peptic ulcer. Patient 092.016.00034 had GI hemorrhage associated with severe underlying disease that included IDDM, CHF and renal failure. Patient 040.004.00103 had a UGI bleed that was diagnosed as secondary to gastritis based upon the findings from endoscopy.

Renal Failure

Patient 040.002.00023 was hospitalized for "renal disorders" by a different physician. Apparently, SKB was unable to get further information. Patient 053.026.00910 had severe CHF and apparently pre-renal azotemia. Patient 053.043.00212 had a stroke followed by acute renal failure and pulmonary embolus. Patient 043.073.01630, a 70 year old male, died during compassionate use study 090 from multiple system failure resulting from cerebral embolism and was also coded with acute renal failure.

Serious Laboratory Abnormalities

Patient 056.011.00258 was a 64 Y/O female who was at dose level 8 with routine laboratory results indicated a markedly elevated CPK . Repeat testing found levels as high as 944 IU/ml (ULN = 200 IU/ml). She was asymptomatic and was hospitalized for work-up. EMG and all other laboratory tests were normal. A muscle biopsy was not

performed and a fractionated CPK was not reported. The patient continued ropinirole and completed the study.

Patient 043.010.01085 also had elevated CPKs that according to the narrative summary were shown to be muscular in origin. LDH was also found to be slightly increased. On workup he was found to have hypothyroidism with both CPK and LDH returning to normal with replacement therapy. He continued on ropinirole. There were no other increases in CPK that were coded as a serious. In addition, there were no other laboratory abnormalities that were coded as serious AEs that weren't associated with a concomitant disease process. There was 1 patient diagnosed with SIADH that had hyponatremia noted at hospitalization for orthopedic surgery.

4.12 AEs Associated with a Change in Ropinirole Dose

AEs that were associated with a reduction in ropinirole were generally similar to the pattern seen with discontinuations. In ET patients, the five most common AEs associated with a ropinirole dose reduction were nausea (13.4%), dizziness (6%), somnolence (4.7%), vomiting (4.3%) and hallucination (2.1%). In AT patients, the five most common AEs associated with a ropinirole dose reduction were dyskinesia (7.2%), hallucination (4.8%), nausea (4.7%), dizziness (4.5%) and insomnia (2.1%). [9]

4.13 AE Risks Associated with Ropinirole Use Irrespective of Severity

4.13.1 Overall

4.13.1.1 ET Patients

SKB table 7.2 lists AEs that were reported in ≥ 5% of ET patients across all treatment groups showing the corresponding risks for each group for the selected AE. The five most common AEs reported in ET patients using ropinirole were nausea (47.6%), dizziness (24.1%), somnolence (22.3%), headache (12.8%), and vomiting and insomnia (both at 12.2%). When RRs are calculated from the absolute risks shown in Table 7.2 (ropinirole compared to each treatment group), the RRs for leg edema and syncope had the largest most consistent differences across treatment groups. Hallucination, which was reported in 6.2% of ropinirole ET patients, was also reported in 6.6% of bromocriptine ET patients.

SKB Table 7.7 lists AEs that were reported in ≥1% of ET patients assigned ropinirole in placebo controlled ET studies. The five most common AEs that were also at least 2

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[9] Percentages of the 515 ropinirole ET and 849 ropinirole AT patients who were dose reduced for this AE occurrence.

times more frequent with ropinirole than placebo were nausea (59.9%), somnolence (39.5%), syncope (11.5%), fatigue (10.8%) and viral infection (10.8%).

In study 054, the following AEs were reported in at least 1% of ropinirole patients and were twice as frequent as with placebo: nausea (52.6%), somnolence (36.2%), syncope (10.3%), fatigue (9.5%), viral infection (8.6%), abdominal pain (6.0%), orthostatic hypotension (6.0%), confusion (6.0%), led edema (6.0%), palpitation (4.3%), asthenia (4.3%), and anorexia (3.4%).

4.13.1.2 AT Patients

SKB Table 7.3 lists AEs that were reported in ≥ 5% of AT patients across treatment groups showing the corresponding risks for each group for the selected AE. The five most common AEs reported with ropinirole's use in AT patients were dyskinesia (26.3%), nausea (25.6%), dizziness (18.7%), worsening of PD (16.4%) and insomnia (14.6%). There were no AEs associated with ropinirole use in AT patients that were consistently larger across all treatment groups.

Table 7.8 lists AEs reported in ≥ 1% of AT patients assigned ropinirole from placebo controlled AT studies. The most common AEs reported with ropinirole that were also twice as frequent as with placebo were dyskinesia (28.5%), confusion (6.7%), anxiety (5.7%), tremor (5.7%) and increased sweating (5.7%).

In the 044 study report, a 1% table was not provided. In the 10% table, dyskinesia (33.7%) was the only AE that was reported twice as frequently as with placebo (SKB Table 23 in Appendix 3).

4.13.2 Dose Response

4.13.2.1 Dose Response in ET Patients

According to its title, SKB Table 15.3 shows the effect of dose on AE risk for AEs that were reported in at least 20% of ET patients using ropinirole. Table 15.3 show absolute risks for dizziness, nausea, somnolence, orthostatic hypotension, syncope, amnesia and hallucination. Because some of these AEs occur less frequently than 20%, the AE selection criteria specified for the table appear to have not been followed.

In any case, for dizziness, nausea, somnolence, syncope and amnesia, the largest risk reported was during daily doses ranging from 1.1 to 4.5 mg. For orthostatic hypotension, a sightly larger risk was reported at daily doses of 4.6 to 7.5 mg compared to that at lower doses. For hallucination, the largest risk was reported when patients were taking daily doses of ≥ 18 mg.

In study 054, a specific dose response analysis was not performed.

4.13.2.2 Dose Response in AT Patients

SKB Table 15.4 shows the effect of dose on selected AEs in AT patients following a similar approach as in ET patients. As before, it is not clear what AE selection criteria were used. The AEs shown include dyskinesia, nausea, orthostatic hypotension, confusion and hallucination. As in ET patients, the largest risk for hallucination was reported at daily doses ≥ 18 mg. For the other AEs, the largest risk was reported at daily doses of 1.1 to 4.5 mg.

In study 044, a dose response analysis was not performed.

4.13.3 AE Occurrence and Plasma Concentration

Ropinirole plasma concentration was not measured at the time of AE occurrence in either ET or AT patients. According to the sponsor, predicted plasma concentration in either patient group was not associated with AE occurrence.

4.13.4 AE Risk by Time Since First Exposure

According to SKB, Tables 7.10 and 7.11 show risks for AEs reported in ≥ 10% of ET and AT patients using ropinirole by time since first exposure. However, as in Tables 15.3 and 15.4 that described dose response, it is unclear what AE selection criteria were actually used since some of the AEs have risk less than 10%. In general, the findings agree with those observed for dose.

4.13.5 AE Risk and Concurrent Medication Use

SKB examined the effect of concurrently use medications on AE risk that might be attributable to ropinirole for both ET and AT patients. AEs were selected if reported in at least 5% of a study population and concurrent medications were selected if their extent of was at least 10%. The concurrent medications selected were selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricylic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and tocopherol.

As previously described in section 3, SKB showed absolute risks for treatment groups with and without concurrent use of the suspect medication. While SKB somewhat addressed attributable risk by examining and differences for ropinirole users to

compared to that in other treatment groups[10] it was difficult to review SKB findings. For seligiline and HCTZ concurrent use, we tried to calculate RRs for each AE show in the SKB tables in both ET and AT patients. However, the table providing absolute AE risk for users and nonusers of HCTZ could not be found.

4.13.5.1 AE Risk and Concurrent Medication Use In ET Patients

When examining the RRs (ropinirole compared to mostly placebo) for users of seligiline compared to corresponding RRs in non-users, there were few overall differences. The most notable difference was observed for dyspepsia, nausea and vomiting where the RRs were several fold smaller in seligiline users compared to non-users.

For HCTZ, according to SKB's interpretation, there was little difference in absolute risks for ropinirole between HCTZ users and nonusers. During beta blocker use, ropinirole risk appeared to be increased for ataxia (falls and impaired balance) and hallucination compared to nonuse.

SKB also examined variation in risk for amantadine, anticholinergic, NSAIDs, beta blockers, ASA and estrogen use. In general, the extent of use in non-ropinirole ET patients was limited reducing power to find any real differences. With hallucinations reported in ropinirole users, the attributable risk appeared to increased in patients using anticholinergic

4.13.5.2 AE Risk by Concomitant Medications In AT Patients

When RRs were examined in AT patients who used selegiline and compared to non-users, there were no significant difference in ropinirole risk.

According to SKB, AT patients who were users of both HCTZ and ropinirole, had increased absolute risk for injury (25.0% vs 9.2%), orthostatic hypotension (27.1% vs 9.9%), ataxia (includes postural instability and falls) (27.1% vs 8.0%), dizziness (33.3% vs 17.9%), nausea (37.5% vs 24.8%), back pain (16.7% vs 5.7%) hallucination (20.8% vs 10.6%). Apparently, similar differences were seen in placebo for dizziness and with bromocriptine for nausea.

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[10] In general, the search for risk modifiers should focus on either the attributable or RR by describing the variation in either for patients with the potential modifier compared to those patients without. Focusing on the absolute risks for ropinirole patients with the potential modifier dose not speak to modification since the same effect could also have occurred for placebo.

No striking increases were reported for the other medications examined.

4.13.6 AE Risk by Age, Gender and Race

There was little variation in attributable and relative AE risks for ropinirole compared to placebo by gender. In ropinirole users > = 75 years of age, there appeared to be increased risk for syncope. There were too few non-white users to examine variation in risk by race.

4.13.7 AE Risk for Selected Underlying Diseases

To describe any potential modification in ropinirole risk for patients with selected underlying diseases, SKB used a similar approach to that with concurrently used medications and for demographic subgroups. The concurrent diseases selected for study were anxiety, conduction disorders, constipation, depression , diabetes, hypertension, insomnia and ischemic heart disease. As before, absolute AE risks within treatment groups were shown for patients with and without that concurrent disease. In addition to the difficulties in reviewing the findings presented by this approach, the meaning of concurrent disease was not clearly described in the ISS and it was possible that some of concurrent diseases should have been AEs.

For most concurrent diseases including baseline history of hallucinations, there were too few patients to make relevant comparisons. In ET patients who reported hypertension, the risk attributable to ropinirole for syncope and hallucinations appeared increased compared to patients without hypertension. In AT patients, there was little difference in any RRs between patients with and without reported hypertension.

4.14 AE Risk During Tapering

There were no significant differences in the AEs reported during tapering although there seemed to be more AEs consistent with worsening of PD. It was difficult to compare risks with placebo since all patients had been counted in each denominator and because some patients entered extension risk were difficult to interpret.

4.15 Changes in Laboratory Parameters Associated with Ropinirole Use

While SKB shows the percentages of patients that were identified by their laboratory flagging procedures, follow-up was limited to patients having at least 2 extreme values or those classified as having AEs. Thus, follow-up for patients with any laboratory abnormality was limited.

Hematology

The proportion of patients with normal baseline levels of hemoglobin, hematocrit and RBC counts who had low endpoint levels was greater with ropinirole than placebo but comparable to that in the active comparator group. There were no differences in the proportion of patients moving from normal to abnormal between ropinirole and any treatmetn groups for counts of platelets, WBCs, neutrophils, lymphocytes, basophils, eosinophils or monocytes in either ET or AT patients.

SKB Table 13.14 shows the percentage of ropinirole patients with an least 1 extreme hematologic laboratory parameter. SKB provided follow-up for the 4 patients who had extreme values of more than parameter shown in Table 13.14. Of these 4 patients, two withdrew from study at the time that the corresponding laboratory abnormally was observed.

Patient 036.002.00016 was a 74 Y/O female who had normal baseline lab. On day 29 at a dose of 4 mg BID, the Hg and Hct were 6.9 and 22, respectively. These values remained abnormal until day 73 when the patient was withdrawn. No clinical details of the workup or subsequent outcome were provided. Patient 043.032.00629 had low Hg, Hct and platelet count with gangrene at day 282 and was withdrawn from study. No other details were available. Patient 056.017.00385 had extreme values for hemoglobin and RBC counts but finished the study. He was a 71 Y/O male who probably had non-insulin dependent diabetes and peripheral vascular disease. His hyperglycemia and anemia remained stable during study and he had serious AEs that were related to several hospitalizations- 1 for confusion and falling, the other for removal of toes. Patient 036.002.00015 also had extreme values for a low hematocrit and RBC count and high lymphocytes and WBC count. No follow-up was available.

Table 13.16 shows hematologic AEs for all patients exposed to ropinirole. There were no striking differences with placebo or with other treatment groups. Based upon our review of serious AEs and deaths there were no cases of aplastic anemia or agranulocytosis, however, there 5 patents with leukocytosis with no follow-up provided. Because we could not find a listing of all AEs, irrespective of severity that were associated with dropout, it was possible that a patient could have dropped out with leucocytosis with no clinical follow-up.

Blood Chemistry Parameters

The proportion of patients who moved from normal to a high level of AST, ALT, alkaline phosphatase , GGT, or total bilirubin ranged from about 2-5% of ropinirole patients and was similar to that in other treatment groups. About 3% and 8% of Ropinirole patients had high levels of creatinine and BUN after having normal baseline levels and was also similar to that observed in other treatmetn groups. About 4% or ropinirole patients had a high uric acid level compared to about 1% of placebo and 7% in other treatment groups. There were no consistent changes in electrolytes or with albumin, total protein, glucose or LDH.

SKB Table 13.15 shows the number of patients with extreme values (For liver enzymes, the value was 4*ULN). Consistent with the shift tables, the percentage of patients with an extreme creatinine was higher with ropinirole with 8 patients having such a value. There was 1 ropinirole patients who had liver enzymes increased more than 4*ULN. As with hematology, follow-up was provided for the 5 patients with extreme values in more than 1 parameter. Four of these patients had concomitant diabetes including the patient with increased hepatic enzymes and three of these four had markedly increased creatinine. The Patents PIDs were 040.004.00103, 043.007.01369, 043.085.01661,056.011.00263, 056.012.00286.

In SKB Table 13.17, AEs associated with abnormalities in blood chemistry are shown. There were two patients who had AE coded as acute renal failure, both were reviewed in section 4.11. Otherwise, there were no striking differences with placebo or active comparators.

4.16 Changes in Vital Signs Associated with Ropinirole Use

There were no significant differences in the percentages of patients with at least 1 measurement of pulse, supine diastolic and systolic BP, or standing diastolic and systolic BP that was considered a value of potential clinical concern. There was little difference between treatment groups in the incidence of orthostatic hypotension. As mentioned earlier, most studies did not time BP measurement to the last study drug dose. A specific list of patients withdrawn for vital sign abnormalities was not provided in the NDA, although, according to SKB, such dropouts were infrequent.

4.17 Changes in ECG Parameter Associated with Ropinirole Use

Across the development program, there were no consistent changes in ECG or AEs that suggesting that ropinirole caused effects on cardiac function. In study 054, which had the most extensive ECG monitoring, there were no differences in incidence of any changes in ECG between ropinirole and placebo.

4.18 Abnormal Involuntary Movement

The abnormal involuntary movement scale (AIMS) was used by investigators to characterize the severity of abnormal movements in AT patients. SKB Table 11.1 shows the risk for exhibiting involuntary movements by time since randomization and including the risk observed during baseline. There was little difference over time with ropinirole, but both placebo and bromocriptine showed a decline.

4.19 Review of Special Studies

4.19.1 Withdrawal Potential

In the US studies 054 and 044, SKB analyzed the data during the 7 day tapering period and in the week thereafter for any evidence of withdrawal in both Ropinirole and placebo patients. There were increases in symptoms associated with PD, but little else. In the follow-up period, there 3 patients reported insomnia (1.4%) who were assigned ropinirole and while there were no reports with placebo. Insomnia was also defined as one of the "concurrent diseases" and it is not clear exactly how insomnia that may have been a "concurrent disease" differed from insomnia as an AE, if there was a difference.

4.19.2 Interaction Studies

According to SKB, co-administration of CYP1A2 substrates, such as caffeine, theophylline and phenacetin, could result in a pharmacokinetic interaction, as these drugs would compete for the same route of elimination as ropinirole. Based upon the expected ropinirole doses to be used in therapy, SKB concluded that it is more likely that these CYP1A2 substrates would influence ropinirole clearance rather than vice-versa. In addition, CYP1A2 inhibitors such as ciprofloxacin can be expected to decrease the clearance of ropinirole on co-administration.

4.20 Human Reproduction Data

No pregnancy exposures were observed with ropinirole. In preclinical studies, embryo toxicity, demonstrated by post-implantation loss, late embryonic deaths and decreased fetal weights, and teratogenicity, demonstrated by digit malformations, were observed in the rat at dosages of 120 and 150 mg/kg.

4.21 Human Carcinogenectity Potential

Hypoprolactinemia in the rat was associated with a reduction in the number of LH receptors on the Leydig cell. According to SKB, prolactin does not appear to modulate Leydig cell function in man as it does in the rat. Leydig cells in the rat express high levels of prolactin receptors, while human Leydig cells may not express the prolactin

receptor at all. In SKB's opinion, it is unlikely that ropinirole could induce proliferative Leydig cell lesions in humans.

In the development program, a 37-year old male was diagnosed with early Stage II embryonal cell carcinoma, 8 months after completing 1 year of treatment with ropinirole in a placebo-controlled early therapy study.

4.22 Overdose Experience

A total of 27 patients accidently took more than their prescribed dose of ropinirole. All were considered as overdoses, although only 10 patients received a dose greater than 24 mg/day. One patient took 25 mg as a single dose and experienced dizziness, sweating and claustrophobia. The highest overdose reported was 435 mg taken over a 7 day period (62.1 mg/day); there were no reported adverse experiences associated with this overdose. Of the remaining 9 patients who received a dose greater than 24 mg/day, 1 patient experienced mild oro-facial dyskinesia, 1 patient experienced intermittent nausea and 7 patients reported no adverse experiences. Other symptoms reported with accidental overdoses were agitation, increased dizziness, grogginess, sedation, orthostatic hypotension, chest pain, confusion, vomiting and nausea. Patient 040.001.00055 had orthostatic hypotension and chest pain that followed a 7 mg dose instead of a 4 mg dose. The event resolved after 2 hours. His BP changed from 126/82 to 80/40.

5 Summary of the Safety Experience in the Ropinirole Development Program

5.1 General Comments

Overall, the ropinirole development program has included adequate short and long-term ropinirole use to evaluate its safety separately in ET and AT patients. There appears to have been enough experience at 24 mg per day, the maximum recommended dose, to evaluate the relative safety of that dose.

Overall, follow-up of patients was good with few patients lost to follow-up. The clinical data provided was sufficient in most cases to describe the general character of most treatment emergent AEs although most phase 2/3 studies did not collect BP data according to time of last dose.

One limitation in the presentation of the data was unclear follow-up for patients with abnormal laboratory values that were not associated with a serious AEs or death. Patients could have dropped from study with a laboratory abnormality and we would have not have known it from the data presented in the ISS. Another limitation in the presentation of the AE findings was difficulty in reviewing any increase in ropinirole risk in selected sub-groupings of patients such for users of selected concurrent

medications.

Overall, ropinirole was tolerated better in AT patients than ET patients. In the US ET study, overall study dropout, AE dropout and risk for serious AEs were all about 2 times more frequent with ropinirole than placebo while there was little difference between ropinirole and placebo in the US AT study.

The events that were reported in more than 5% of ropinirole ET patients that were at least 2 times more frequent than in placebo were nausea, somnolence, fatigue, viral infections, abdominal pain, syncope, orthostatic hypotension, confusion and leg edema. In AT patients, across all AT placebo controlled studies in the ISS, dyskinesia, increased sweating, anxiety, tremor and confusion were reported in more than 5% of ropinirole patients and were at least 2 times more frequent than in placebo. Most treatment emergent AEs that are associated with ropinirole use can be grouped under the cardiovascular and neurological systems and are discussed further below.

5.2 Cardiovascular System

In clinical pharmacology studies, ropinirole caused a consistent dose related reduction in standing BP at 1 and 2 hours post-dose when compared to placebo. At 1 hour following a 1 mg dose, the mean decreases of standing systolic and diastolic BP were 15 and 10 mm Hg, respectively. The effect of ropinirole on standing pulse was not as consistent. After a 1 mg dose, the mean standing pulse decreased 8 beats per minute (bpm) at 1 hour, but at 2 hours, there was a mean increase of 15 bpm. While 47 PD patient volunteers were also included in phase 1 studies, the NDA did not clearly describe whether similar changes in BP and pulse were also observed in patient volunteers, and if so, at what doses.

Of the 110 healthy volunteers, 9 had either orthostatic hypotension or were so symptomatic on standing that BP could not be measured. There were 2 similar events in patient volunteers. One healthy volunteer had full clinical recovery following orthostatic hypotension, syncope and 26 seconds of asystole that occurred 1 hour after a 1 mg dose when standing for a BP measurement. Ropinirole did not prolong the QT interval or cause any evidence of dysrhythmia other than the bradycardia that was observed 1 hour post-dose and in most patients who had orthostatic hypotension.

As noted above, in the US ET study, study dropout and AE dropouts were about 2 times more frequent with ropinirole than placebo with several of these events CV in nature and consistent with ropinirole's CV effects that were observed in animals and in healthy volunteers. The CV events that were most strongly associated with ropinirole use in ET patients were orthostasis as reflected by increased syncope, orthostatic symptoms with most syncopal events associated with bradycardia, and leg edema

suggesting that venous pooling may result from ropinirole use.

Of the 22 serious AEs in study 054, six were CV in nature with several patients hospitalized following syncope and/or orthostatic hypotension associated with bradycardia. Syncope had the largest relative difference in risk when compared to placebo in study 054; 10.3% (12 events) compared to 1.6% (2 events). Three of the 12 syncope events were associated with study dropout. While no objective evidence of orthostatic hypotension was observed in study 054, BP measurement was not timed to last dose.

In the US AT study 044, ropinirole exposure was not associated with increases in study dropout, either overall or that associated with an AE, or increased risk for serious AEs when compared to placebo. None of the 15 patients exposed to ropinirole who had serious AEs had syncope, bradycardia or orthostatic hypotension and only 1 patient had an event that could be considered CV in nature. There was no clear pattern of AEs that was associated with dropout. There were no deaths in ropinirole patients in study 044, and across all AT patients in the ISS, ropinirole mortality was less than that in any other treatment group. Syncope was reported in 3.2% of ropinirole AT patients compared to 1.2% in placebo patients.

Despite the increase of CV events in ET patients taking ropinirole, there were no deaths in study 054, and across the NDA, mortality was significantly lower with ropinirole than any other treatment group providing some reassurance that while ropinirole has CV effects, there was no suggestion of increased mortality resulting from its use.

In addition, the dose escalation scheme proposed and used by SKB does not eliminate the possibility of CV events. In study 054, the difference between ropinirole and placebo in the frequency of study dropout was mostly explained by differences occurring between 10 and 20 weeks of study. Since most dropouts were related to an AE occurrence, this difference probably reflected an increased AE risk over this period. Although an AE analysis by week of study and the dose at dropout was not provided for study 054, the increase in frequency of dropout increased over this period should have correlated with daily doses of 4.5 mg or more.

Since studies 054 and 044 both excluded most patients with significant underlying CV disease, the expected effect in such patients is unknown. While examining the effect of ropinirole in patients taking HCTZ or hypertension was a good thought, the presentation of the data for this analysis was difficult to follow. Perhaps SKB could re-analyze 054 and 044 developing a definition of underlying CVD and then calculate relative risks across strata for the AEs of interest.

In summary, the CV effects appear to result from ropinirole dopaminergic activity causing orthostatic type symptoms as documented in phase 1 studies and suggested by

an increased risk of syncope in both ET and AT patients. There was no evidence in animal or humans that ropinirole affected cardiac conduction other than the bradycardia observed in animals and humans associated with orthostasis.

5.3 Central Nervous System

In addition to clear CV effects from ropinirole, CNS events were also increased during is use in animals and humans. In particular hallucinations and confusion were associated with ropinirole use in both ET and AT patients. Somnolence was also noted in phase 1 volunteers and in phase 2/3 studies. While confusion was reported in more than 5% of ET and AT patients, it clinical nature and outcome were not well defined in the ISS.

In animal studies, ropinirole was shown to bind to the kappa receptor. There was no evidence of opiate-type withdrawal during tapering in phase 2/3 studies and animal studies designed to investigate withdrawal potential were negative.

5.4 Dermatological

There was no increase in the risk for rash. However, there were 2 cases of hospitalized serious skin reactions that reported in ropinirole treated patients. Both were not well described clinically.

5.5 Gastrointestinal

In the pre-clinical studies, gastric hemorrhage was observed in rates treated with ropinirole at high dose. In the phase 2/3 studies, there were a few events of GI hemorrhage with one reported to be secondary to gastric hemorrhage. Considering the age of the population studies, such an observation does not seem unexpected.

Abdominal pain was reported frequently in ET patients. There was little clinical information for the nature of such complaints.

While there were no cases of retroperitoneal fibrosis, there was limited study power given its rarity.

5.6 Genitourinary/Renal

A decrease in uric acid secretion was observed In phase 1 studies. In phase 2/3 studies, both ropinirole and the active comparison groups had higher percentages of patients with increased uric acid levels than in placebo. There were no cases of urolithiasis reported but the power of the development program to detect such would seem to be limited. There were no cases of gout noted in the ISS, but searches for cases of possible

gout or use of uricosuric agents were was not performed.

5.7 Hematologic

There were no hematologic effects associated with ropinirole use. There was one case of life-threatening thrombocytopenia that was purported to be caused by an immune mechanism although little clinical information was provided for this case.

5.8 Metabolic Endocrine

Serum prolactin was decreased in both animals and humans during use of ropinirole similar to that seen with other dopamine agonists.

5.9 Musculoskeletal

There were no cases of rhabdomyolysis.

5.10 Respiratory

No evidence of pulmonary fibrosis, but given the rarity of that event, the data base had limited power to have observed any cases.

5.11 Special Senses

There were no specific occur findings. However, some follow-up of the cases of ocular abnormalities in study 054 is needed.

6 Conclusion

Ropinirole use in US ET patients was associated with increased risks for serious AEs and AE dropouts with the clinical nature of several of these AEs consistent with ropinirole's CV effects observed in Phase 1 healthy volunteers and in preclinical studies. While there was a clear increase in CV events attributable to ropinirole there were no deaths in study 054 and across the ISS, overall mortality was less with ropinirole than any other treatment group. While there was increased risk for non-CV and CV events in AT patients, the events were not as severe. Considering the low prevalences of underlying CV disease and CV medication use in study 054, the labeling should warn that ropinirole has significant CV effects and has not been studied in patients who are both candidates for ET and who have moderate or severe CV disease. Such warning should also be considered for AT patients since study 044 also excluded patients who had moderate or severe CV disease. Phase 4 study of ropinirole's use in patients with underlying CV disease could delineate any increased risk.

6.1 Suggested Follow-up Issues

(1) Using a definition of CVD based upon medication use and reported underlying CVD at baseline, re-analyze studies 054 and 044 calculating RRs for patients with CVD and compare those to RRs in patients without evidence of CVD.

(2) Provide follow-up for all patients meeting F3 and F4 laboratory flags.

(3) Describe the CV effects on the patient volunteers in the phase 1 studies. For example, the change in standing BP by dose.

(4) Provide a description of occular abnormalities observed in studies 054 and 032.

(5) Clinical describe the abdominal pain reported in US study 054.

(6) Clinical describe the events coded as confusion in US study 054 and 044. In addition discuss the outcomes from these events.

(7) Explore the data base for gout or use of uricosuric agents.

7 Labeling Recommendations

(1) The sponsor's claim in labeling that the risk of orthostatic hypotension was no different with ropinirole than placebo seems unsubstantiated and should be deleted.

(2) Take out the part about retroperitoneal fibrosis, the data base had limited power to make such a claim.

(3) Under precautions "Ropinirole has significant potential to cause orthostatic hypotension. Its effects in patients with underlying CVD have not been studied." Consider making this a warning.

10-11-96

Greg Burkhart, M.D., M.S.

Appendix 1

SKB Tables from the ISS that were Referenced in the Safety Review

Table 2.1 Table of Investigations

Study Number CPMS	Country/ Centers	Calender Dates	Objectives	Study design	Treatment*	Dose (mg)/ Frequency	Duration	N
Clinical Pharmacology Studies - Healthy Volunteers								
001	UK/1	07 JUL 87 03 NOV 87	An assessment of the safety and effects on prolactin and cardiovascular function of oral administration of a range of doses of a solution of ropinirole in healthy male volunteers	Single-blind placebo controlled dose rising	Ropinirole Placebo	0.01, 0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 1.0, 1.25, 1.85, 2.5 od	3 Single doses of active drug and one placebo 48 hours apart	14
002	US/1	12 SEP 88 21 APR 89	Effect of ropinirole on renal function in healthy subjects	Single blind cross -over	Ropinirole Placebo	0.2, 0.4 od	3 days apart	6
003	UK/1	09 NOV 87 14 DEC 87	A study of the effect of oral ropinirole on supine and erect blood pressure and plasma catecholamines in healthy male volunteers	Single-blind placebo-controlled dose rising	Ropinirole Placebo	0.25, 0.5, 1.0 od	5 days apart	6
004	Germany/1	24 NOV 87 16 DEC 87	A study to assess the effects of ropinirole and hemadynamic and neuroendocrine function in supine resting condition and in response to adrenergic stimulation in subjects	Placebo-controlled single-blind cross over	Ropinirole Placebo	0.4, 0.8, 1.0 od	6 days apart	8
005	US/1	05 APR 88 12 DEC 88	To assess the CNS effects of ropinirole in normal volunteers using quantitative pharmaco-EEG and topographical colored dynamic brain mapping techniques	Double-blind, placebo-controlled crossover	Ropinirole Diazepam Amitripty-line Placebo	0.2, 0.4, 0.6, 0.8 od 5 50 od	3 days apart	12

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008	UK/1	16 MAY 88 14 JUL 88	An assessment of the safety and effects on serum prolactin and cardiovascular function of acute iv infusion of a range of doses of ropinirole in healthy male volunteers	Single-blind placebo controlled dose rising	Ropinirole IV Placebo	0.04 , 0.08 0.12 od	48 hours apart	5
009	Germany/1	19 FEB 92 21 MAR. 92	A study to investigate the tolerance and preliminary pharmacokinetics of intravenous doses SKF 101468 following domperidone pre-treatment (20 mg t.i.d.). in healthy male volunteers	Open	Ropinirole IV + domperidone	GpA 0.1, 0.2, 0.4, GpB 0.2 0.6, 0.8 GpC 0.4, 0.6, 0.8 od	7 days apart	17
010	Germany/1	01 AUG 88 05 SEP 88	The effects of a single dose of 20mg domperidone (Domp) on the pharmacokinetic, safety and pharmacodynamic responses to an oral dose of SKF 101468 in healthy volunteers	Double-blind crossover	Ropinirole Placebo Domperi-done	Domp + 0.8 or Domp + placebo or Placebo + 0.8 od	7 days apart	10
011	UK/1	18 OCT 88 10 JAN 89	A study to investigate the pharmacokinetics and to profile the metabolites of 14C labeled ropinirole when administered by the iv and oral route to healthy male volunteers	Open 2 way, crossover	Ropinirole oral IV	0.6 0.08 od	28 days apart	4
012	Germany/1	09 MAY 89 30 MAY 89	A study to assess the acute effects of a standard meal on the plasma pharmacokinetics of ropinirole, after administration of a single oral dose of ropinirole in normal man	Open randomized, 2-way crossover	Ropinirole	0.8 fed and fasted od	7 days apart	12
061	Germany/1	11 MAY 92 29 MAY 93	A study to investigate the relative and absolute	Open, randomized, three-way crossover	Ropinirole IV	0.8	7 days apart	17

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			bioavailability of ropinirole following domperidone pre-treatment in healthy male volunteers		Tablet Solution	1.0 1.0 od		
Clinical Pharmacology - Patient Volunteers								
007	UK/1	01 JUN 88 30 JUL 88	A study to assess the effects of SK&F 101468 in the treatment of Parkinson's disease	Double-blind, placebo-controlled, dose-rising	Ropinirole Placebo	0.2, 0.4, 0.6, 0.8, 1.0 od	48 hours apart	6
016	**Italy/1**	**18 APR 94 27 JAN 95**	**A study to investigate the impact of ropinirole at steady state on plasma concentration of digoxin in Parkinsonian patients**	**Open**	**Ropinirole Digoxin**	**Titrated 0.25 to 2 tid 0.1 to 0.3 od**	**6 weeks**	**10**
018	Germany/1	11 JUL 88 11 JUL 89	A study to assess the effects of ropinirole in the treatment of Parkinson's disease	Double-blind, placebo-controlled dose rising	Ropinirole Placebo	Gp1 0.2, 0.4, 0.6, Gp2 0.8, 1.4, 2.0, Gp3 2.0, 4.0, 6.0 od	48 hours apart	12
019	UK/1	28 NOV 88 31 MAY 89	A study to assess the effects of ropinirole and domperidone in the treatment of Parkinson's disease	Double-blind, placebo-controlled, single-dose rising	Ropinirole Placebo	1.0, 1.6, 2.4, 3.2, 4.0, 5.0 od	48 hours apart	8
021	France/1	21 MAY 89 08 JUN 90	A study to assess the effects of ropinirole in the treatment of Parkinson's disease	Open, single-dose rising	Ropinirole	1.0. 2.0, 4.0. 6.0, 8.0, 10 od	7 days	8
027	**Italy/1**	**31 JAN 90 30 JUN 91**	**A study to assess pharmacokinetic interaction between single doses of SK&F 101468 and l-dopa**	**Double-blind, placebo-controlled, cross-over**	**Ropinirole ± l-dopa**	**0.2, 0.6 od + Sinemet**	**6 days**	**9**
057	Sweden/1	09 SEP 92 08 APR 94	To assess the antiparkinson activity using optoelectronic movement analysis and	Double-blind, single dose rising study	Ropinirole	2 -12 od randomized	3 x single dose	13

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053	Belgium/2 Switz/2 France/4 Germany/5 Hungary/8 Israel/3 Italy/7 Holland/1 Scandanavia/4 UK/1 S Africa/1	24 NOV 92 (6 month interim) ONGOING	A study of ropinirole at a flexible dose for 3 years in the symptomatic treatment of early Parkinsonian patients not treated with L-dopa	Double-blind, bromocriptine controlled, parallel group, dose titration, multicenter	Ropinirole Bromocrip-tine Ratio 1:1	Titrated 0.25 to 8.0 tid 1.25-13.3 mg tid	3 years with 6 month efficacy analysis	335
054	US/25	27 AUG 92 30 SEP 94	A double-blind, placebo controlled study of oral doses ropinirole for 6 months treatment as early therapy inParkinsonian patients not receiving dopaminergic therapy	Double-blind, placebo-controlled, parallel group , dose titration study multicenter	Ropinirole Placebo Ratio 1:1	Titrated 0.25 -8.0 tid	6 months	241
055	US/22	22 MAR 93 ONGOING	A double-blind, placebo controlled, parallel group study of oral doses of ropinirole for 6 more months treatment as early therapy in Parkinsonian patients - Extension of Study 054	Double-blind, placebo-controlled, parallel group	Ropinirole Placebo	Up to 8.0 tid	6 months	147
056Φ	Belgium/3 Canada/4 France/5 Israel/3 Italy/5 Holland/1 UK/10	22 JUL 92 (6 month interim) ONGOING	A study of ropinirole at a flexible dose for 5 years in the symptomatic treatment of early Parkinsonian patients	Double-blind, L-dopa controlled, parallel group, dose titration multicenter	Ropinirole L-dopa Ratio 2:1	Titrated 0.25 -8.0 tid 50-400 mg tid	5 years with 6 month efficacy analysis	268 31Φ

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058	**Finland/1**	**27 JAN 93 ONGOING**	**A study to assess the safety and clinical efficacy of ropinirole as monotherapy vs placebo for up to 5 years in de novo patients with Parkinson's disease**	**Double-blind, placebo controlled, parallel group**	**Ropinirole** **Placebo**	**Titrated 0.25-8.0 t.i.d**	**5 years with 12 month efficacy analysis**	**100**
093	**Belgium/3 France/4 Italy/3 UK/4**	**02 MAR 95 ONGOING**	**A study to assess rapid dose escalation of ropinirole with and without domperidone**	**Double-blind, parallel group, multicenter**	**Ropinirole + domperidone Ropinirole + placebo**	**Titrated 0.25-8.0 t.i.d**	**3 months**	**125**
Adjunct Therapy Studies								
020	UK/1	01 NOV 88 14 FEB 89	A study to assess the safety, pharmacokinetic profile and efficacy of chronic administration of ropinirole in patients with Parkinson's disease	Open dose rising	Ropinirole	0.6 bid or 0.6, 1.0 bid or 0.6, 1.0, 1.4 bid or 0.6, 1.0, 1.4, 2.0 bid	7 days at each dose	9
023	UK/3 SA/2	21 MAY 89 20 APR 90	A study to assess anti-Parkinson activity of ropinirole given as adjunct therapy in L-dopa treated patients with PD	Open	Ropinirole	Titrated 0.6 to 8.0 bid	6-8 weeks	51
030	UK/1 France/1	26 MAR 90 31 AUG 91	A study to assess the anti-Parkinson efficacy of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa	Double blind placebo controlled, dose titration, parallel group	Ropinirole Placebo Ratio 1:1	Titrated 0.5 to 4.0 bid	12 weeks	46
031	UK/1	20 JUL 90	A study to assess the	Double blind	Ropinirole	up to 12.0	9 months	25

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	France/1	15 MAY 92	anti-Parkinson's efficacy and safety of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa - Extension of study 030	placebo controlled parallel group	Placebo	bid		
034	UK/6 Israel/2	28 AUG 90 30 SEP 91	A study to assess the anti-Parkinson efficacy (L-dopa sparing effect) of ropinirole vs placebo as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa	Double blind placebo controlled, dose titration, parallel group	Ropinirole Placebo Ratio 2:1	Titrated 0.5 to 5.0 bid	12 weeks	68
035	UK/6 Israel/2	15 DEC 90 15 JUL 92	A study to assess the anti-Parkinson's efficacy (L-dopa sparing effect) and safety of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa - Extension of study 034	Double blind, placebo controlled, parallel group	Ropinirole Placebo	up to 12.0 bid	9 months	41
036	Holland/1 S Africa/1 Italy/1 Belgium/2 France/1	03 AUG 90 31 AUG 91	A study to assess the antiparkinson efficacy of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa	Double blind placebo controlled, dose titration, parallel group	Ropinirole Placebo Ratio 2:1	Titrated 0.5 to 5.0 bid	12 weeks	29
037	S Africa/1	23 OCT 90 15 JUN 92	A study to assess the antiparkinson efficacy and	Double blind, placebo controlled,	Ropinirole	Up to 12.0 bid	9 months	21

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	Italy/1 Belgium/2 France/1		safety of ropinirole versus placebo as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa - Extension of Study 036	parallel group	Placebo			
038	Belgium/1 Italy/1 Spain/1 UK/1 S Africa/1	04 JUL 90 31 OCT 91	A study to assess the antiparkinson efficacy of ropinirole versus placebo as adjunct therapy in Parkinsonian patients experiencing late stage complex on/off fluctuations	Double blind, placebo controlled, dose titration, parallel group	Ropinirole Placebo Ratio 2:1	Titrated 0.5 to 4.0 bid	12 weeks	36
039	Belgium/1 Italy/1 Spain/1 UK/1 S Africa/1	15 OCT 90 15 JUL 92	A study to assess the antiparkinson efficacy and safety of ropinirole versus placebo as adjunct therapy in Parkinsonian patients experiencing late stage complex on/off fluctuations - Extension of Study 038	Double blind placebo controlled parallel group	Ropinirole Placebo	Up to 12.0 bid	9 months	21
040	US/15	15 SEP 91 30 OCT 92	Ropinirole 0.5 mg b.i.d, 1.0 mg b.i.d. or 2.0 mg b.i.d versus placebo as adjunct to L-dopa in the treatment of Parkinson's disease	Double blind placebo controlled parallel group	Ropinirole Placebo	0.5 bid or 1.0 bid or 2.0 bid	4-8 weeks	125
041	US/14	10 JAN 92 31 OCT 94	Ropinirole as adjunct to L-dopa (DCI) in the treatment of Parkinson's disease Extension of study 040	Open	Ropinirole	0.5 to 6.0 bid or tid	2 years	97
043	Belg/15 Canada/5	20 NOV 92 18 OCT 94	A double-blind, bromocriptine-controlled,	Double blind, bromocriptine	Ropinirole	Titrated 0.25 to	6 months	555

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	Switz/2 Spain/2 France/15 Germany/4 Israel/5 Italy/5 Holland/3 Portugal/3 Scandin-avia/4 UK/4 S Africa/2		multicenter study of ropinirole at a flexible oral dose for 6 months in the treatment of Parkinsonian patients not optimally controlled on levodopa	controlled,parallel group, dose titration, double dummy	Bromo-criptin e Ratio 2:1	8 tid 1.25- 40 mg TDD		
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044	US/16	24 SEP 92 30 SEP 94	A study of oral doses of ropinirole for 6 months treatment as adjunct therapy in Parkinsonian patients not optimally controlled on L-dopa (DCI)	Double blind, placebo controlled, dose titration, parallel group	Ropinirole Placebo Ratio 2:1	Titrated 0.25 to 8 tid	6 months	149
050	Belg/12 Canada/5 Switz/2 Spain/2 France/14 Germany/4 Israel/5 Italy/4 Holland/3 Portugal/3 Scandin-avia/3 UK/4 S Africa/2	15 MAY 93 ONGOING	A study of ropinirole at a flexible dose for six more months in the treatment of Parkinsonian patients not optimally controlled on L-Dopa (DCI) - Extension of Study 043	Double-blind, bromocriptine controlled, multicenter	Ropinirole Bromo-criptine	Up to 8.0 tid	6 months	402
			APPEARS THIS WAY ON ORIGINAL			APPEARS THIS WAY ON ORIGINAL		
051	US/15	07 APR 93	A study of ropinirole for six more months as adjunct	Placebo controlled, multicenter, parallel	Ropinirole	Up to 8.0 tid	6 months	75

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		ONGOING	therapy in Parkinsonian patients not optimally controlled on L-dopa (DCI) - Extension of Study 044	group	Placebo			
092	US/5	06 MAR 92 ONGOING	Pharmacokinetic assessment of ropinirole under multiple dosing steady state conditions in Parkinson's disease	Open	Ropinirole	0.5 - 6.0 bid/tid	2 years	23
099	France/16 Hungary/4 Italy/3	07 JUN 94 ONGOING	An study to assess the safety and efficacy of ropinirole at a flexible dose of 0.25mg-8 mg three times a day for one year in Parkinsonian patients not optimally controlled on L-dopa.	Open	Ropinirole	Up to 8.0 tid	1 year	85
Compassionate Use								
026	UK/2	27 JUL 89 31 JAN 91	Compassionate use of ropinirole as adjunct to L-dopa in Parkinson's disease - from Study 023	Open	Ropinirole	Up to 10 bid		9
090	Any in program	15 MAR 92 ONGOING	Compassionate use continuation of double blind medication from ropinirole Phase II and III studies or compassionate administration of open-label ropinirole in the treatment of Parkinson's disease.	Open or Double-blind	Ropinirole (Some active controls)	Up to 8.0 tid		106

* All doses were oral unless indicated otherwise
TDD= total daily dose
Studies 016, 062, 063, 027, 058, 093 and non-core 056Φ are included for reporting of serious adverse experiences (Section 8.H.8) and deaths (Section 8.H.9). Studies 058 and 093 were ongoing double-blind studies at clinical cut-off of October 31, 1994. ΦNon-core 056 patients (n=31) were enrolled after the clinical cut-off for the PET portion of this study. Study 027 although completed is not contained on the database. Studies 016, 062, and 063 were

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ongoing clinical pharmacology studies at the clinical cut-off. In addition to serious adverse experiences and deaths, the specific interaction results are described (Section 8.H.16).

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Table 4.4a

Overall Exposure by Mean Total Daily Dose of Ropinirole in Therapeutic Studies - Early Therapy Studies

	Ropinirole (Total Daily Dose mg)															
	0		0.1 - 1.0		1.1 - 4.5		4.6 - 7.5		7.6 - 12.0		12.1 - 18.0		>= 18.1	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<=1 week	0		8	50.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
2 - 4 weeks	0		6	37.5	9	8.9	0	0.0	0	0.0	0	0.0	0	0
5 - 8 weeks	0		2	12.5	12	11.9	3	2.0	1	0.9	0	0.0	0	0
9 - 12 weeks	0		0	0.0	12	11.9	7	4.7	1	0.9	0	0.0	0	0
13 - 24 weeks	0		0	0.0	11	10.9	23	15.3	7	6.1	4	4.3	0	0
25 - 48 weeks	0		0	0.0	30	29.7	56	37.3	34	29.6	34	37.0	6	14
49 - 96 weeks	0		0	0.0	24	23.8	53	35.3	66	57.4	50	54.3	33	80
97 - 144 weeks	0		0	0.0	3	3.0	8	5.3	6	5.2	4	4.3	2	4
>=145 weeks	0		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Total	0		16	100.0	101	100.0	150	100.0	115	100.0	92	100.0	41	100

Table 4.4b

Overall Exposure by Mean Total Daily Dose of Ropinirole in Therapeutic Studies - Adjunct Therapy Studies

	Ropinirole (Total Daily Dose mg)													
	0		0.1 - 1.0		1.1 - 4.5		4.6 - 7.5		7.6 - 12.0		12.1 - 18.0		>= 18.1	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<=1 week	0		11	23.4	4	1.9	3	1.5	1	0.5	1	0.7	0	0
2 - 4 weeks	0		31	66.0	37	17.8	4	2.1	1	0.5	0	0.0	0	0
5 - 8 weeks	0		5	10.6	65	31.3	8	4.1	3	1.5	2	1.4	0	0
9 - 12 weeks	0		0	0.0	30	14.4	21	10.8	3	1.5	2	1.4	0	0
13 - 24 weeks	0		0	0.0	28	13.5	29	14.9	10	4.9	9	6.1	4	8
25 - 48 weeks	0		0	0.0	26	12.5	79	40.7	86	42.4	51	34.5	18	36
49 - 96 weeks	0		0	0.0	14	6.7	42	21.6	75	36.9	68	45.9	27	55
97 - 144 weeks	0		0	0.0	4	1.9	8	4.1	24	11.8	15	10.1	0	0
>=145 weeks	0		0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0
Total	0		47	100.0	208	100.0	194	100.0	203	100.0	148	100.0	49	100

Table 5.7 Concurrent Illnesses (>5% of any treatment group) by WHO Disease Classification - Early Therapy Study Population

	Ropinirole N=515		Placebo N=147		L-Dopa N=89		Bromocriptine N=167	
Preferred Term	n	%	n	%	n	%	n	%
Hypertension	119	23.1	14	9.5	22	24.7	49	29.3
Insomnia	37	7.2	10	6.8	6	6.7	10	6.0
Prostate Disorder	33	6.4	6	4.1	6	6.7	15	9.0
Depression	31	6.0	11	7.5	5	5.6	8	4.8
Diabetes Mellitus	30	5.8	6	4.1	7	7.9	14	8.4
Ischemic Heart Disease	27	5.2	2	1.4	4	4.5	19	11.4
Back Pain	23	4.5	12	8.2	1	1.1	9	5.4
Constipation	23	4.5	14	9.5	4	4.5	9	5.4
Arthropathy	20	3.9	12	8.2	1	1.1	3	1.8
Dyspepsia	9	1.7	10	6.8	1	1.1	3	1.8

Data Source Table 5.1a

Table 5.8 Concurrent Illnesses (>5% in any treatment group) by WHO Disease Classification Body System - Adjunct Therapy Study Population

	Ropinirole N=849		Placebo N=151		Bromocriptine N=188	
Preferred Term	n	%	n	%	n	%
Insomnia	114	13.4	24	15.9	31	16.5
Depression	105	12.4	17	11.3	25	13.3
Hypertension	88	10.4	19	12.6	33	17.6
Constipation	85	10.0	15	9.9	17	9.0
Anxiety	65	7.7	13	8.6	19	10.1
Arthropathy	46	5.4	19	12.6	5	2.7
Prostate Disorder	41	4.8	1	0.7	13	6.9
Osteoarthrosis	36	4.2	7	4.6	10	5.3
Hernia, Abdominal	34	4.0	9	6.0	6	3.2
Diabetes Mellitus	31	3.7	5	3.3	12	6.4
Back Pain	26	3.1	9	6.0	7	3.7
Conduction Disorder	20	2.4	8	5.3	7	3.7

Data Source Table 5.1b

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Table 6.1 Discontinuations from Ropinirole by Individual Study

Study Number (CPMS)	Country	Number Exposed to Ropinirole	Completed		Completed/ Entered Extension		OngoingΨ		Adverse Experience		Lack of Efficacy		Otherφ	
		N	n	%	n	%	n	%	n	%	n	%	n	%
Clinical Pharmacology Studies - Healthy Volunteers														
001	UK	14	14	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
002	USA	6	5	83.3	0	0.0	0	0.0	0	0.0	0	0.0	1	16.7
003	UK	6	6	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
004	Germany	8	8	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
005	USA	12	12	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
008	UK	5	5	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
009	Germany	17	15	88.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
010	Germany	9	9	100	0	0.0	0	0.0	0	0.0	0	0.0	2	11.8
011	UK	4	4	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
012	Germany	12	12	100	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
061	Germany	17	14	82.4	0	0.0	0	0.0	2	11.8	0	0.0	1	5.9
Clinical Pharmacology Studies - Patient Volunteers														
007	UK	6	5*	80.0	0	0.0	0	0.0	1	20.0	0	0.0	0	0.0
018	Germany	12	11	91.7	0	0.0	0	0.0	0	0.0	0	0.0	1	8.3
019	UK	8	6*	75.0	0	0.0	0	0.0	2	25.0	0	0.0	0	0.0
021	France	8	3	37.5	0	0.0	0	0.0	5	62.5	0	0.0	0	0.0
057	Sweden	13	9	69.2	0	0.0	0	0.0	4	30.8	0	0.0	0	0.0
Therapeutic Studies														
Early Therapy Studies														
022	UK	11	7	63.6	0	0.0	0	0.0	4	36.4	0	0.0	0	00
032	Europe S. Africa	41	9	22.0	27	65.9	0	0.0	3	7.3	0	0.0	2	4.9
033	Europe S. Africa	(27)	15	55.6	3**	11.1	0	0.0	4	14.8	2	7.4	3	11.1
053	Europe S. Africa	168	0	0.0	0	0.0	126	75.0	21	12.5	4	2.4	17	10.1
054	USA	116	9	7.8	70	60.3	0	0.0	27	23.3	1	0.9	9	7.8
055	USA	(70)	46	65.8	5**	8.5	15	21.1	3	4.7	0	0.0	1	1.4

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056	Europe	179	0	0.0	0	0.0	140	78.2	26	14.5	6	3.4	7	3.9
Adjunct Therapy Studies														
020	UK	9	8	88.9	0	0.0	0	0.0	1	11.1	0	0.0	0	0.0
023	UK S. Africa	49 [2]	30	58.8	9** 3⊗	25.5	0	0.0	7 1⊗	15.7	0	0.0	1	2.0
030	UK France	23	4	17.4	17	73.9	0	0.0	1	4.3	1	4.3	0	0.0
031	UK France	(17)	8	47.1	3**	17.6	0	0.0	4	23.5	1	5.9	1	5.9
034	UK Israel	44 (2)	3	6.5	28	60.9	0	0.0	8	17.4	4	8.7	3	6.5
035	UK Israel	(28)	14	50.0	5**	17.9	0	0.0	6	21.4	0	0.0	3	10.7
036	Europe S. Africa	19 (1)	2	10.0	15	75.0	0	0.0	3	15.0	0	0.0	0	0.0
037	Europe S. Africa	(15)	7	46.8	3**	20.0	0	0.0	2	13.3	2	13.3	1	6.7
038	Europe S. Africa	23 (1)	3 1⊗*	16.7	13	54.2	0	0.0	3	12.5	1	4.2	3	12.5
039	Europe S. Africa	(13)	5	38.5	3**	23.1	0	0.0	2	15.4	1	7.7	2	15.4
040	USA	90	6	6.7	77	85.6	0	0.0	7	7.8	0	0.0	0	0.0
041	USA	23 (74)	33	34.0	16**	16.5	0	0.0	18	18.6	18	18.6	12	12.4
043	Europe S. Africa	367	36	9.8	263	71.7	0	0.0	49	13.4	12	3.3	7	1.9
044	USA	95	22	23.2	52	54.7	0	0.0	15	15.8	4	4.2	2	2.1
050	Europe S. Africa	(263)	90	34.2	45**	17.1	106	40.3	12	4.6	7	2.7	3	1.1
051	USA	(52)	34	65.4	4**	7.7	5	9.6	5	9.6	0	0.0	4	7.7
092	USA	20 (3)	0	0.0	0	0.0	17	73.9	0	0.0	6	26.1	0	0.0
099	Europe	85	0	0.0	0	0.0	79	92.9	3	3.5	2	2.4	1	1.2
Compassionate Use														
026	UK	(9)	1	11.1	5**	55.6	0	0.0	2	22.2	1	11.1	0	0.0
090	Europe USA S. Africa	14 (92)	0	0.0	0	0.0	100	94.3	5	4.7	1	0.9	0	0.0

Study Numbers in Italics indicate extension studies.

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Number in parenthesis ( ) indicate patients counted in a previous therapeutic study.
Number in brackets [ ] indicates patients counted in a previous patient volunteer study. These patients are counted in the therapeutic study population and patient volunteer study populations, but are counted only once in the All Patients Exposed population.
* Includes 1 patient who completed this study and later entered a therapeutic study, see Section 3.2 for details.
**Patients entered into compassionate use. These patients are counted as ongoing in Table 6.2 but are considered as completed in Tables 6.3, 6.4 and 6.5.
⊗ Patients completed this study and entered a second therapeutic study; one of these patients (PID 023.001.01002) withdrew due to an AE but entered study 038, as PID 038.002.00013. This patient is considered completed in Table 6.2.
⊗* Patient 023.001.01002/038.002.00013 completed study 038 but is counted as withdrawn due to adverse experience in Tables 6.3 and 6.5.
Ψ Patients ongoing at clinical cut-off, October 31, 1994.
φ Includes deviation from protocol and lost to follow-up.

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Table 6.4 Discontinuations by Reason - Early Therapy Study Population

	Ropinirole N=515		Placebo N=147		L-Dopa N=89		Bromocriptine N=167	
Reason	n	%	n	%	n	%	n	%
Completed	94	18.3	95	64.6	0	0	0	0
Ongoing	281	54.6	18	12.2	74	83.2	130	77.8
Discontinuations								
Adverse Experience	88	17.1	19	12.9	14	15.7	25	15.0
Lack of Efficacy	13	2.5	7	4.8	1	1.1	3	1.8
Deviation from Protocol	17	3.3	2	1.4	0	0.0	2	1.2
Lost to follow-up	9	1.8	1	0.7	0	0.0	4	2.4
Other	13	2.5	5	3.4	0	0.0	3	1.8

Data Source Table 6.1b

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Table 6.5 Discontinuations by Reason - Adjunct Therapy Study Population

	Ropinirole N=849		Placebo N=151		Bromocriptine N=188	
Reason	**n**	**%**	**n**	**%**	**n**	**%**
Completed	393	46.3	62	41.1	88	46.8
Ongoing	207	24.4	30	19.9	58	30.9
Discontinuations						
Adverse Experience	147	17.3	24	15.9	29	15.4
Lack of Efficacy	59	7.0	28	18.5	8	4.3
Deviation from Protocol	18	2.1	1	0.7	2	1.1
Lost to follow-up	8	0.9	0	0.0	3	1.6
Other	17	2.0	6	4.0	0	0.0

Data Source Table 6.1c

Table 7.10 Emergent adverse experiences (≥ 10% overall based on the ropinirole group) by time-
Early Therapy Study Population

	Time Interval									
	≤ 4 weeks		5-12 weeks		13-24 weeks		25-48 weeks		≥ 49 weeks	
ROPINIROLE	N = 515		N = 492		N = 454		N = 409		N = 249	
	n	%	n	%	n	%	n	%	n	%
Dizziness	41	8.0	45	9.1	22	4.8	14	3.4	2	0.8
Headache	36	7.0	13	2.6	7	1.5	10	2.4	0	0.0
Nausea	102	19.8	103	20.9	23	5.1	13	3.2	4	1.6
Vomiting	12	2.3	28	5.7	9	2.0	12	2.9	2	0.8
Insomnia	9	1.7	24	4.9	16	3.5	12	2.9	2	0.8
Somnolence	33	6.4	41	8.3	19	4.2	18	4.4	4	1.6
PLACEBO	N = 147		N = 142		N = 126		N = 112		N = 57	
	n	%	n	%	n	%	n	%	n	%
Dizziness	10	6.8	8	5.6	8	6.3	6	5.4	0	0.0
Headache	9	6.1	5	3.5	7	5.6	4	3.6	0	0.0
Nausea	11	7.5	11	7.7	7	5.6	3	2.7	0	0.0
Vomiting	3	2.0	4	2.8	2	1.6	1	0.9	0	0.0
Insomnia	7	4.8	2	1.4	3	2.4	6	5.4	0	0.0
Somnolence	2	1.4	2	1.4	2	1.6	3	2.7	0	0.0
L-DOPA	N = 89		N = 86		N = 81		N = 78		N = 57	
	n	%	n	%	n	%	n	%	n	%
Dizziness	3	3.4	6	7.0	3	3.7	1	1.3	0	0.0
Headache	5	5.6	6	7.0	1	1.2	1	1.3	0	0.0
Nausea	16	18.0	9	10.5	5	6.2	2	2.6	4	7.0
Vomiting	0	0.0	2	2.3	3	3.7	2	2.6	0	0.0
Insomnia	3	3.4	4	4.7	2	2.5	3	3.8	2	3.5
Somnolence	3	3.4	5	5.8	6	7.4	3	3.8	0	0.0
BROMOCRIPTINE	N = 167		N = 159		N = 151		N = 139		N = 84	
	n	%	n	%	n	%	n	%	n	%
Dizziness	11	6.6	6	3.8	10	6.6	4	2.9	1	1.2
Headache	10	6.0	9	5.7	2	1.3	0	0.0	2	2.4
Nausea	16	9.6	16	10.1	3	2.0	4	2.9	2	2.4
Vomiting	2	1.2	3	1.9	2	1.3	2	1.4	1	1.2
Insomnia	6	3.6	2	1.3	1	1.3	4	2.9	2	2.4
Somnolence	7	4.2	2	1.3	2	1.3	0	0.0	0	0.0

Data Source Table 7.2a

Table 7.11 Emergent adverse experiences (≥ 10% overall based on the ropinirole group) by time -
Adjunct Therapy Study Population

	Time Interval									
	≤ 4 weeks		5-12 weeks		13-24 weeks		25-48 weeks		≥ 49 weeks	
ROPINIROLE	N = 849		N = 756		N = 617		N = 537		N = 277	
	n	%	n	%	n	%	n	%	n	%
Injury	13	1.5	19	2.5	20	3.2	21	3.9	13	4.7
Hypotension postural	30	3.5	34	4.5	14	2.3	9	1.7	5	1.8
Dizziness	72	8.5	55	7.3	15	2.4	10	1.9	7	2.5
Dyskinesia	73	8.6	77	10.2	42	6.8	25	4.7	6	2.2
Parkinsonism Aggravated	23	2.7	41	5.4	31	5.0	30	5.6	14	5.2
Headache	45	5.3	24	3.2	18	2.9	7	1.3	1	0.4
Nausea	108	12.7	72	9.5	24	3.9	10	1.9	3	1.1
Insomnia	31	3.7	34	4.5	20	3.2	29	5.4	10	3.6
Somnolence	36	4.2	32	4.2	10	1.6	14	2.6	5	1.8
Hallucination	17	2.0	22	2.9	18	2.9	33	6.1	5	1.8
PLACEBO	N = 151		N = 141		N = 88		N = 58		N = 30	
	n	%	n	%	n	%	n	%	n	%
Injury	3	2.0	3	2.1	4	4.5	2	3.4	0	0.0
Hypotension postural	11	7.3	5	3.5	2	2.3	2	3.4	0	0.0
Dizziness	10	6.6	7	5.0	2	2.3	2	3.4	0	0.0
Dyskinesia	9	6.0	9	6.4	0	0.0	1	1.7	0	0.0
Parkinsonism Aggravated	8	5.3	10	7.1	3	3.4	6	10.3	1	3.3
Headache	9	6.0	1	0.7	1	1.1	3	5.2	0	0.0
Nausea	13	8.6	10	7.1	0	0.0	2	3.4	1	3.3
Insomnia	7	4.6	6	4.3	2	2.3	5	8.6	0	0.0
Somnolence	5	3.3	7	5.0	0	0.0	0	0.0	0	0.0
Hallucination	0	0.0	3	2.1	1	1.1	1	1.7	1	3.4
BROMOCRIPTINE	N = 188		N = 179		N = 163		N = 148		N = 68	
	n	%	n	%	n	%	n	%	n	%
Injury	2	1.1	2	1.1	2	1.2	4	2.7	0	0.0
Hypotension postural	2	1.1	4	2.2	5	3.1	3	2.0	0	0.0
Dizziness	9	4.8	9	5.0	5	3.1	5	3.4	0	0.0
Dyskinesia	9	4.8	20	11.2	4	2.5	7	4.7	0	0.0
Parkinsonism Aggravated	7	3.7	6	3.4	5	3.1	6	4.1	0	0.0
Headache	4	2.1	2	1.1	0	0.0	5	3.4	0	0.0
Nausea	10	5.3	8	4.5	4	2.5	4	2.7	0	0.0
Insomnia	4	2.1	2	1.1	7	4.3	7	4.7	0	0.0
Somnolence	4	2.1	3	1.7	3	1.8	2	1.4	0	0.0
Hallucination	2	1.1	5	2.8	5	3.1	6	4.1	0	0.0

Data Source Table 7.2b

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Table 7.18 Adverse experiences leading to discontinuation of ≥ 1% of patients in any treatment group - Early Therapy Study Population

	Ropinirole N = 515		Placebo N = 147		L-Dopa N = 89		Bromocriptine N = 167	
	n	%	n	%	n	%	n	%
Cardiovascular General								
Hypertension	3	0.6	2	1.4	0	0.0	1	0.6
Syncope	3	0.8	0	0.0	1	1.1	0	0.0
Central and Peripheral Nervous System								
Dizziness	7	1.4	2	1.4	1	1.1	0	0.0
Dyskinesia	3	0.6	0	0.0	1	1.1	0	0.0
Headache	3	0.6	3	2.0	0	0.0	1	0.6
Parkinsonism aggravated	7	1.4	1	0.7	0	0.0	1	0.6
Gastrointestinal System								
Diarrhea	1	0.2	1	0.7	2	2.2	0	0.0
Dyspepsia	2	0.4	1	0.7	1	1.1	3	1.8
Nausea	21	4.1	2	1.4	3	3.4	4	2.4
Vomiting	9	1.7	1	0.7	2	2.2	3	1.8
Myocardial Endocardial Pericardial Valve								
Angina Pectoris	2	0.4	2	1.4	0	0.0	0	0.0
Psychiatric								
Anxiety	3	0.6	1	0.7	1	1.1	0	0.0
Confusion	2	0.4	0	0.0	1	1.1	2	1.2
Hallucination	9	1.7	0	0.0	1	1.1	4	2.4

Data Source Table 7.8B

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Table 7.19 Adverse experiences leading to discontinuation of ≥ 1% of patients in any treatment group - Adjunct Therapy Study Population

	Ropinirole N = 849		Placebo N = 151		Bromocriptine N = 188	
	n	%	n	%	n	%
Cardiovascular General						
Hypotension Postural	5	0.6	3	2.0	1	0.5
Central and Peripheral Nervous System						
Ataxia	1	0.1	1	0.7	3	1.6
Dizziness	10	1.2	0	0.0	2	1.1
Dyskinesia	12	1.4	2	1.3	1	0.5
Parkinsonism Aggravated	10	1.2	2	1.3	2	1.1
Gastrointestinal System						
Dyspepsia	3	0.4	0	0.0	2	1.1
Nausea	17	2.0	0	0.0	0	0.0
Vomiting	10	1.2	0	0.0	3	1.6
Metabolic and Nutritional						
Dehydration	0	0.0	0	0.0	2	1.1
NPN Increased	0	0.0	0	0.0	2	1.1
Psychiatric						
Confusion	11	1.3	2	1.3	2	1.1
Hallucination	27	3.2	2	1.3	3	1.6

Data Source Table 7.8c

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Table 7.2 Emergent adverse experiences (incidence ≥ 5% in any treatment group) - Early Therapy Study Population

	Ropinirole N = 515		Placebo N = 147		L-dopa N = 89		Bromocriptine N = 167	
	n	%	n	%	n	%	n	%
Autonomic Nervous System								
Sweating Increased	21	4.1	6	4.1	5	5.6	1	0.6
Body as a Whole General								
Fatigue	39	7.6	6	4.1	2	2.2	8	4.8
Edema Legs	33	6.4	1	0.7	2	2.2	3	1.8
Pain	31	6.0	6	4.1	5	5.6	3	1.8
Asthenia	29	5.6	2	1.4	3	3.4	4	2.4
Edema Dependent	21	4.1	5	3.4	1	1.1	10	6.0
Injury	20	3.9	12	8.2	6	6.7	12	7.2
Cardiovascular General								
Hypotension Postural	36	7.0	7	4.8	7	7.9	18	10.8
Syncope	35	6.8	2	1.4	4	4.5	4	2.4
Central/Peripheral Nervous System								
Dizziness	124	24.1	32	21.8	13	14.6	32	19.2
Headache	66	12.8	25	17.0	13	14.6	23	13.8
Tremor	32	6.2	17	11.6	3	3.4	5	3.0
Parkinsonism aggravated	26	5.0	9	6.1	7	7.9	12	7.2
Ataxia	24	4.7	9	6.1	5	5.6	7	4.2
Dyskinesia	13	2.5	10	6.8	10	11.2	2	1.2
Gastrointestinal System								
Nausea	245	47.6	32	21.8	36	40.4	41	24.6
Vomiting	63	12.2	10	6.8	7	7.9	10	6.0
Dyspepsia	50	9.7	7	4.8	13	14.6	8	4.8
Abdominal Pain	42	8.2	4	2.7	9	10.1	18	10.8
Constipation	30	5.8	11	7.5	6	6.7	15	9.0
Anorexia	20	3.9	2	1.4	5	5.6	5	3.0
Diarrhea	13	2.5	7	4.8	6	6.7	6	3.6
Musculoskeletal System								
Back Pain	39	7.6	16	10.9	7	7.9	8	4.8
Arthralgia	34	6.6	17	11.6	4	4.5	5	3.0
Myalgia	18	3.5	8	5.4	2	2.2	1	0.6
Psychiatric								
Somnolence	115	22.3	9	6.1	17	19.1	11	6.6

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Insomnia	63	12.2	18	12.2	14	15.7	16	9.6
Hallucination	32	6.2	2	1.4	3	3.4	11	6.6
Anxiety	23	4.5	13	8.8	5	5.6	13	7.8
Depression	22	4.3	10	6.8	9	10.1	10	6.0
Amnesia	9	1.7	2	1.4	5	5.6	2	1.2
Paranoia	5	1.0	1	0.7	5	5.6	1	0.6
Resistance Mechanism								
Infection Viral	42	8.2	5	3.4	8	9.0	10	6.0
Upper Respiratory Tract Infection	32	6.2	25	17.0	4	4.5	1	0.6
Respiratory System								
Bronchitis	12	2.3	2	1.4	5	5.6	10	6.0
Urinary System								
Micturition Frequency	3	0.6	8	5.4	0	0	0	0

Data Source Table 7b

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Table 7.3 Emergent adverse experiences (incidence ≥ 5% in any treatment group) - Adjunct Therapy Study Population

	Ropinirole N = 849		Placebo N = 151		Bromocriptine N = 188	
	n	%	n	%	n	%
Autonomic Nervous System						
Sweating Increased	46	5.4	2	1.3	7	3.7
Mouth Dry	33	3.9	2	1.3	10	5.3
Body as a Whole General						
Injury	86	10.1	12	7.9	10	5.3
Asthenia	37	4.4	10	6.6	5	2.7
Cardiovascular General						
Hypotension Postural	92	10.8	20	13.2	14	7.4
Central/Peripheral Nervous System						
Dyskinesia	223	26.3	19	12.6	40	21.3
Dizziness	159	18.7	21	13.9	28	14.9
Parkinsonism Aggravated	139	16.4	28	18.5	24	12.8
Headache	95	11.2	14	9.3	11	5.9
Ataxia	77	9.1	10	6.6	16	8.5
Tremor	50	5.9	5	3.3	12	6.4
Gastrointestinal System						
Nausea	217	25.6	26	17.2	26	13.8
Abdominal Pain	58	6.8	10	6.6	19	10.1
Vomiting	58	6.8	6	4.0	13	6.9
Dyspepsia	50	5.9	6	4.0	16	8.5
Constipation	47	5.5	7	4.6	25	13.3
Musculoskeletal System						
Back Pain	54	6.4	7	4.6	12	6.4
Arthralgia	49	5.8	8	5.3	6	3.2
Myalgia	44	5.2	7	4.6	9	4.8
Psychiatric						
Insomnia	124	14.6	20	13.2	20	10.6
Somnolence	97	11.4	12	7.9	12	6.4
Hallucination	95	11.2	6	4.0	18	9.6
Confusion	60	7.1	2	1.3	10	5.3
Anxiety	46	5.4	3	2.0	8	4.3
Depression	40	4.7	8	5.3	6	3.2
Resistance Mechanism						

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Infection Viral	45	5.3	9	6.0	14	7.4
Upper Respiratory Tract Infection	43	5.1	11	7.3	6	3.2

Data Source Table 7c

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Table 7.5 The number and percent of dosing sessions (≥ 1% on ropinirole) during which emergent adverse experiences occurred - Healthy Volunteer Study Population

	All Ropinirole* N=302		All Placebo N=63		Others** N=24	
	n	%	n	%	n	%
Headache	28	9.3	5	7.9	0	0
Nausea	25	8.3	0	0	0	0
Dizziness	17	5.6	1	1.6	0	0
Hypotension Postural	9	3.0	1	1.6	0	0
Sweating Increased	7	2.3	1	1.6	0	0
Extrasystoles Supraventricular	3	1.0	2	3.2	0	0
Malaise	6	2.0	0	0	0	0
Fatigue	5	1.7	1	1.6	0	0
Yawning	4	1.3	0	0	0	0
Hot Flushes	4	1.3	0	0	0	0
Bradycardia	4	1.3	0	0	0	0
Vomiting	4	1.3	0	0	0	0
Flushing	3	1.0	0	0	0	0
Abdominal Pain	3	1.0	0	0	0	0

N=Total number of subject sessions
* Includes oral and intravenous ropinirole, with and without domperidone
** Others= Diazepam, Amitriptyline
Data Source Table 7i

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Table 7.7 Emergent adverse experiences occurring in 1% or more of patients on ropinirole - Early Therapy Placebo-Controlled Studies

	Ropinirole N = 157		Placebo N = 147	
	n	%	n	%
Autonomic Nervous System				
Flushing	5	3.2	1	0.7
Mouth Dry	8	5.1	5	3.4
Sweating Increased	10	6.4	6	4.1
Body as a Whole General				
Asthenia	10	6.4	2	1.4
Cellulitis	2	1.3	0	0.0
Chest Pain	5	3.2	3	2.0
Drug Level Increased	7	4.5	4	2.7
Edema Dependent	10	6.4	5	3.4
Edema Legs	10	6.4	1	0.7
Fever	2	1.3	2	1.4
Fatigue	17	10.8	6	4.1
Hot Flushes	4	2.5	5	3.4
Injury	6	3.8	12	8.2
Malaise	5	3.2	1	0.7
Pain	12	7.6	6	4.1
Rigors	2	1.3	2	1.4
Therapeutic Response Decreased	3	1.9	1	0.7
Cardiovascular General				
Hypertension	6	3.8	5	3.4
Hypotension	3	1.9	0	0.0
Hypotension Postural	10	6.4	7	4.8
Syncope	18	11.5	2	1.4
Central and Peripheral Nervous System				
Ataxia	6	3.8	9	6.1
Carpal Tunnel Syndrome	2	1.3	1	0.7
Dizziness	64	40.8	32	21.8
Dyskinesia	5	3.2	10	6.8
Dystonia	2	1.3	3	2.0
Headache	27	17.2	25	17.0
Hyperkinesia	2	1.3	2	1.4
Hypesthesia	6	3.8	3	2.0

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Myalgia	6	3.8	8	5.4
Myocardial Endocardial Pericardial Valve				
Myocardial Ischemia	2	1.3	1	0.7
Neoplasm				
Basal Cell Carcinoma	2	1.3	2	1.4
Psychiatric				
Amnesia	4	2.5	2	1.4
Anxiety	5	3.2	13	8.8
Concentration Impaired	3	1.9	0	0.0
Confusion	8	5.1	2	1.4
Depression	6	3.8	10	6.8
Dreaming Abnormal	2	1.3	3	2.0
Hallucination	8	5.1	2	1.4
Illusion	2	1.3	0	0.0
Insomnia	17	10.8	18	12.2
Nervousness	5	3.2	7	4.8
Somnolence	62	39.5	9	6.1
Yawning	5	3.2	0	0.0
Reproductive Male				
Impotence	4	2.5	2	1.4
Prostatic Disorder	2	1.3	2	1.4
Resistance Mechanism				
Infection Viral	17	10.8	5	3.4
Upper Respiratory Tract Infection	22	14.0	25	17.0
Respiratory System				
Bronchitis	4	2.5	2	1.4
Coughing	2	1.3	4	2.7
Dyspnea	5	3.2	0	0.0
Pharyngitis	10	6.4	6	4.1
Respiratory Disorder	3	1.9	2	1.4
Rhinitis	6	3.8	4	2.7
Sinusitis	6	3.8	4	2.7
Skin and Appendages				
Rash	4	2.5	4	2.7
Urinary System				
Cystitis	2	1.3	1	0.7
Hematuria	2	1.3	2	1.4
Urinary Retention	2	1.3	1	0.7
Urinary Tract Infection	7	4.5	6	4.1
Vascular Extracardiac				
Cramps Legs	6	3.8	7	4.8
Peripheral Ischemia	4	2.5	0	0.0

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Muscle Contractions Involuntary	2	1.3	4	2.7
Paresthesia	6	3.8	6	4.1
Parkinsonism Aggravated	7	4.5	9	6.1
Tremor	12	7.6	17	11.6
Vertigo	3	1.9	0	0.0
Gastrointestinal System				
Abdominal Pain	10	6.4	4	2.7
Anorexia	6	3.8	2	1.4
Colitis	2	1.3	0	0.0
Constipation	13	8.3	11	7.5
Diarrhea	4	2.5	7	4.8
Dyspepsia	15	9.6	7	4.8
Dysphagia	2	1.3	0	0.0
Flatulence	4	2.5	2	1.4
Gingivitis	2	1.3	2	1.4
Nausea	94	59.9	32	21.8
Periodontitis	2	1.3	0	0.0
Saliva Increased	2	1.3	3	2.0
Tooth Disorder	3	1.9	1	0.7
Vomiting	19	12.1	10	6.8
Hearing and Vestibular				
Tinnitus	2	1.3	0	0.0
Heart Rate and Rhythm				
Bradycardia	3	1.9	3	2.0
Extrasystoles	3	1.9	1	0.7
Fibrillation Atrial	2	1.3	0	0.0
Palpitation	5	3.2	3	2.0
Tachycardia	3	1.9	0	0.0
Tachycardia Supraventricular	2	1.3	0	0.0
Liver and Biliary System				
Gamma - GT Increased	2	1.3	1	0.7
Hepatic Enzymes Increased	2	1.3	0	0.0
Metabolic and Nutritional				
Gout	2	1.3	3	2.0
Hyperglycemia	2	1.3	3	2.0
Hypoglycemia	2	1.3	0	0.0
Phosphate Alkaline Increased	3	1.9	2	1.4
Weight Decrease	2	1.3	5	3.4
Musculoskeletal System				
Arthralgia	14	8.9	17	11.6
Arthritis	4	2.5	5	3.4
Back Pain	11	7.0	16	10.9

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Vision				
Eye Abnormality	5	3.2	2	1.4
Vision Abnormal	9	5.7	5	3.4
Xerophthalmia	3	1.9	0	0.0

Data Source Table 7.1e

Table 7.8 Emergent adverse experiences occurring in 1% or more of patients on ropinirole - Adjunct Therapy Placebo-Controlled Studies

	Ropinirole N = 298		Placebo N = 151	
	n	%	n	%
Autonomic Nervous System				
Flushing	5	1.7	2	1.3
Mouth Dry	13	4.4	2	1.3
Sweating Increased	17	5.7	2	1.3
Body as a Whole General				
Asthenia	12	4.0	9	6.0
Chest Pain	4	1.3	4	2.6
Drug Level Increased	14	4.7	4	2.6
Edema Dependent	7	2.3	4	2.6
Edema Legs	4	1.3	1	0.7
Fatigue	5	1.7	6	4.0
Fever	3	1.0	0	0.0
Hot Flushes	3	1.0	2	1.3
Influenza-Like Symptoms	4	1.3	0	0.0
Injury	28	9.4	12	7.9
Malaise	3	1.0	1	0.7
Pain	13	4.4	6	4.0
Cardiovascular General				
Hypertension	8	2.7	4	2.6
Hypotension	5	1.7	1	0.7
Hypotension Postural	33	11.1	20	13.2
Syncope	10	3.4	2	1.3
Central and Peripheral Nervous System				
Ataxia	22	7.4	10	6.6
Dizziness	70	23.5	21	13.9
Dyskinesia	85	28.5	19	12.6
Dystonia	11	3.7	5	3.3
Gait Abnormal	4	1.3	2	1.3
Headache	40	13.4	14	9.3
Hyperkinesia	3	1.0	2	1.3
Hypokinesia	11	3.7	5	3.3
Paresis	6	2.0	0	0.0

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Paresthesia	13	4.4	3	2.0
Parkinsonism Aggravated	47	15.8	28	18.5
Tremor	17	5.7	4	2.6
Vertigo	3	1.0	4	2.6
Gastrointestinal System				
Abdominal Pain	18	6.0	10	6.6
Constipation	13	4.4	7	4.6
Diarrhea	13	4.4	5	3.3
Dyspepsia	14	4.7	6	4.0
Dysphagia	5	1.7	1	0.7
Eructation	3	1.0	0	0.0
Flatulence	4	1.3	1	0.7
Nausea	78	26.2	26	17.2
Periodontitis	3	1.0	1	0.7
Saliva Increased	5	1.7	1	0.7
Tooth Ache	3	1.0	0	0.0
Vomiting	19	6.4	6	4.0
Heart Rate and Rhythm				
Palpitation	7	2.3	2	1.3
Metabolic and Nutritional				
Weight Decrease	6	2.0	1	0.7
Musculoskeletal System				
Arthralgia	16	5.4	8	5.3
Arthritis	5	1.7	1	0.7
Arthritis Aggravated	3	1.0	0	0.0
Back Pain	13	4.4	7	4.6
Myalgia	10	3.4	7	4.6
Neoplasm				
Neoplasm Nos	3	1.0	0	0.0
Psychiatric				
Amnesia	10	3.4	1	0.7
Anxiety	17	5.7	3	2.0
Confusion	20	6.7	2	1.3
Depersonalization	3	1.0	0	0.0
Depression	10	3.4	8	5.3
Dreaming Abnormal	7	2.3	3	2.0
Hallucination	22	7.4	6	4.0
Insomnia	38	12.8	20	13.2
Nervousness	12	4.0	3	2.0
Paranoid Reaction	3	1.0	0	0.0
Paroniria	4	1.3	2	1.3
Somnolence	46	15.4	12	7.9

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Thinking Abnormal	3	1.0	1	0.7
Red Blood Cell				
Anemia	5	1.7	0	0.0
Reproductive Male				
Prostatic Disorder	3	1.0	0	0.0
Resistance Mechanism				
Infection Viral	17	5.7	9	6.0 ND
Upper Respiratory Tract Infection	19	6.4	11	7.3 ND
Respiratory System				
Coughing	4	1.3	1	0.7
Dyspnea	7	2.3	3	2.0
Pharyngitis	3	1.0	2	1.3
Respiratory Disorder	4	1.3	0	0.0
Rhinitis	5	1.7	5	3.3
Skin and Appendages				
Rash	4	1.3	2	1.3
Special Senses Other				
Taste Perversion	3	1.0	3	2.0
Urinary System				
Hematuria	7	2.3	4	2.6
Micturition Frequency	4	1.3	0	0.0
Pyuria	4	1.3	1	0.7
Urinary Incontinence	4	1.3	1	0.7
Urinary Tract Infection	14	4.7	4	2.6 ND
Vascular Extracardiac				
Cramps Legs	5	1.7	5	3.3
Vision				
Cataract	3	1.0	1	0.7
Diplopia	4	1.3	2	1.3
Lacrimation Abnormal	3	1.0	0	0.0
Xerophthalmia	3	1.0	1	0.7
White Cell & Reticuloendothelial System				
Eosinophilia	3	1.0	0	0.0

Data Source Table 7.1f

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