4.6 Extent of Exposure

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

In the 16 completed RCTs, a total of 879 unique patients were exposed to PPX for a total of 274.4 patient years. Table 4.6.1.1 displays patient exposure in patient years:

Table 4.6.1.1 Duration of Patient Exposure in Patient Years Phase II/III Trials

Type of Trial		Pramipexole	Placebo
Phase II/III (Completed PD Trials)	N Patient Years	702 258.8	551 225.5
Phase II/III (Completed Schizophrenia Trials)	N Patient Years	177 15.9	95 9.3
Total Phase II/III Completed Trials	N Patient Years	879 274.4	646 234.8
All Phase II/III Trials-- Completed and Ongoing	N Patient Years	1408 815	

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Appendix 4.6.1.1 is a detailed (separated by disease type) table of the number of patients and estimated Person-Years (PYs) of pramipexole use. PYs were estimated based on the medication records: the exact number of days were computed for each patient and are presented here in 0-24 months, >6-24 months, and >12-24 months intervals.

Overall (including the extension trials that are ongoing), there were 1419 pramipexole patients observed in phase 2/3 studies. Dose information is not available on 11 patients, therefore a total of 1408 patients with 815 PYs of pramipexole use are included in the exposure data, most of it (800 PYs) coming from the PD trials.

4.6.2 Extent of Exposure by Dose

Appendices 4.6.2.1 and 4.6.2.2 show the mean and maximum dose exposures of ET and AT patients by weeks. Table 4.6.2.1 displays the number of pramipexole patients achieving $\geq$ 4.5 mg total daily dose (the maximum dose recommended):

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Table 4.6.2.1
Pramipexole Patients Achieving $\geq$ 4.5 mg Total Daily Dose

Population	Number of Patients Achieving $\geq$ 4.5 mg at any Time During Study	Number of Patients Achieving $\geq$ 4.5 mg for $\geq$ 12 Consecutive Weeks	Total Number of Pramipexole Patients Exposed
Completed Studies			
All Patients	474	190	879
All PD Patients	421	190	702
All AT Patients	176	85	286
All ET Patients	245	105	416
All Schizophrenia Patients	53	0	177
Completed + Ongoing Studies			
All Patients	1034	552	1408
All PD Patients	981	552	1231
All AT Patients	377	248	556
All ET Patients	604	304	675
All Schizophrenia Patients	53	0	177

As the above table indicates, in the phase 2/3 completed and ongoing studies, 1034 of the 1408 patients and 981 of the 1231 PD patients studies achieved the highest dose of 4.5 mg/day (604 ET and 377 AT patients). Of the 1034 patients that reached 4.5 mg/day, 552 were exposed to this dose for more than 12 consecutive weeks. In the completed PD studies, 421 of the 702 PD patients achieved the highest dose of 4.5 mg/day (245 ET and 176 AT patients). Of the 421 patients that reached 4.5 mg/day, 190 were exposed to this dose for more than 12 consecutive weeks.

4.6.3 Extent of Dosing in Selected Demographic Groups

There was no difference in the total daily pramipexole dose between ET and AT patients based on gender or age. 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. Tables 4.6.3.1-4 display these findings:

Table 4.6.3.1. AT Patients: Pramipexole Total Daily Dose (mg) by Sex						
Sex	N	Mean	Std Dev	Std Err	Min	Max
Male	149	3.75	1.30	0.11	0.2	5.0
Female	86	3.56	1.44	0.16	0.375	5.0

Studies Included: M27300010, M27300019, M27300020, M27300022

Table 4.6.3.2. ET Patients: Pramipexole Total Daily Dose (mg) by Sex						
Sex	N	Mean	Std Dev	Std Err	Min	Max
Male	229	3.77	1.49	0.19	0.0	6.0
Female	126	3.57	1.51	0.13	0.375	6.0

Studies Included: M27300001, M27300004, M27300021

Table 4.6.3.3. AT Patients: Pramipexole Total Daily Dose (mg) by Age						
Age	N	Mean	Std Dev	Std Err	Min	Max
$\leq$ 45	11	3.36	1.56	0.47	0.75	5.0
46-55	45	3.70	1.47	0.22	0.2	5.0
56-65	78	3.74	1.32	0.15	0.375	5.0
66-75	87	3.71	1.30	0.14	0.4	5.0
> 75	14	3.33	1.47	0.39	0.375	5.0

Studies Included: M27300010, M27300019, M27300020, M27300022

Table 4.6.3.4. ET Patients: Pramipexole Total Daily Dose (mg) by Age						
Age	N	Mean	Std Dev	Std Err	Min	Max
$\leq$ 45	28	3.91	1.55	0.29	1.5	6.0
46-55	61	3.32	1.59	0.20	0.75	6.0
56-65	108	3.76	1.41	0.14	0.0	6.0
66-75	130	3.83	1.48	0.13	0.0	6.0
> 75	28	3.48	1.57	0.30	0.0	6.0

Studies Included: M27300001, M27300004, M27300021

* Only patients who entered the maintenance interval are included

4.7 Phase 1 Safety

The sponsor has divided the 19 phase 1 studies into 3 types: 3 basic PK studies (29, 30, and 47); 7 studies with "factors affecting PK" (60--ongoing, 61, 62, 63, 64, 65, and 69); and 9 safety and tolerance studies (3, 23, 25, 26, 27, 28, 31, 51, and 73). In the 19 phase 1 studies of the ISS, there were 13 single-dose studies with the pramipexole dose ranging from 0.1-0.4 mg, while in the 6 multiple-dose (with maximum duration of 30 days) studies the pramipexole dose ranged from 0.375-4.5 mg/day. Eight of the single-dose (25, 28, 29, 30, 51, 61, 64, and 65) and 2 of the multiple-dose (62 and 63) were crossover. Four of the studies investigated different pramipexole formulations: study 29 compared pramipexole given intravenously (IV) to an oral solution and a tablet form; study 73 was an eye drop formulation; studies 30 and 62 compared two planned marketed formulations; and study 31 was a transdermal formulation.

All 9 safety and tolerance studies, except for study 73, were conducted in healthy, young males. Study 73, the ocular study, enrolled 6 males and 6 females. The age range in this group was

Two of the basic PK studies were conducted in healthy males, while the other enrolled males and females. The age range in this group was years.

Two of the 7 studies with "factors affecting PK" were conducted in males, another four enrolled males and females, while the age-gender study (60), is currently ongoing and is enrolling elderly (up to 80 years of age) patients of both sexes.

There was only one phase 1 trial with patient (APD) volunteers with N of 3.

Across the phase 1 studies, no deaths or serious AEs were reported.

In the 9 safety and tolerance studies, one placebo patient and 3 pramipexole patients discontinued due to orthostatic hypotension. In studies 25 (single dose), 26, and 3 (both multiple dose), symptomatic orthostatic hypotension (OSH) was identified as a dose-related phenomenon and dose-limiting (maximum tolerated dose of 0.4 mg for study 26). OSH was evident following a single oral dose of 0.2 mg (first dose phenomenon) in study 26.

The time to onset of OSH varied from 30 minutes to 6 hours. The duration of OSH varied from 1 hour or less to at least 8 hours depending upon dose. The magnitude of drug-induced changes in standing blood pressure and pulse rate could not be adequately assessed in all patients because of the inability to stand for vital sign measurements. Changes from baseline observed in the vital signs of three subjects recorded drops in the SBP, DBP, and HR as follows: subject 1, a decrease of 66 mg/Hg in SBP, no change in DBP, and a decrease of 36 bpm in HR; subject 2, a

decrease of 35 mg/Hg in SBP, a decrease of 30 mg/Hg in DBP, and no change in HR (30 minutes after administration of 0.4mg); and subject 3, a decrease of 17 mg/Hg in SBP, a decrease of 26 mg/Hg in DBP, and an increase of 16 bpm in HR. Subject 2 was unable to stand again for 8 hours and continued to experience nausea and asthenia for up to 12 hours. Other symptoms associated with OSH were dizziness, asthenia, malaise, nausea, increased sweating.

There were no clinically significant changes from baseline in ECG parameter reported during the evaluation periods compared with placebo, but one pramipexole patient discontinued due to a "non-serious" atrial tachycardia.

In the 10 PK studies, 9 volunteers discontinued: 1 patient (#26, study 60) for GI bleeding; 2 due to increases in BP; 2 for not feeling well; 1 due to abdominal colic; 1 due to irritability after receiving one dose of Sinemet; and 2 due to nausea and vomiting. In protocol 63, there were 6 patients (#s 1, 3, 5, 7, 9, and 10) who had orthostatic symptoms and 8 patients (#s 1, 2, 3, 5, 7, 8, 9, and 10) who had decreases of systolic BP of more than 20 mm Hg. These changes occurred during the ascending phase of the pramipexole dosing. Also in protocol 65, 2 patients reported dizziness and nausea on standing with some reduction of standing BP at 3 hours post-dosing.

In the safety and tolerance studies, a slight PR interval increase in the ECGs were noted, upon standing.

There were no changes of clinical importance observed in the laboratory parameters. Serum prolactin concentrations were measured in 2 phase 1 studies in healthy volunteers and statistically significant decreases were noted at the first sampling time (30 minutes post dose), maximum effect was reached at 2-4 hours post dose, and were still significantly decreased compared to baseline at 8 hours post dose.

Appendix 4.7.1 summarizes the AEs observed in non-patient volunteers. In these volunteers headache, asthenia, abdominal pain, pain, chills, infection, malaise, back pain, pallor, postural hypotension, vasodilatation, nausea, anorexia, vomiting, constipation, dyspepsia, flatulence, diarrhea, dizziness, nervousness, somnolence, insomnia, concentration impaired, agitation, rhinitis, sweating, pruritis, and decrease in creatinine clearance occurred at a percentage difference of $> 5\%$ (pramipexole n=240 and placebo n=69). There were 3 reports of syncope in the pramipexole treated healthy volunteers and none in the placebo.

4.8 Mortality in Phase 2/3 Studies

4.8.1 Pramipexole Mortality Compared to Placebo

Through January 31, 1995, there were 17 deaths observed in the development program, of which, 15 cases (deaths or the event leading to death) occurred within 30 days of the last dose of pramipexole or placebo. Of the 17 deaths, 14 occurred with pramipexole and of the 14, 10 occurred in the AT studies and 4 in the ET studies. There was 1 pramipexole death within 30 days of last use in study 1, and 3 deaths in study 10. Table 4.8.1.1 shows the estimated mortality rates for pramipexole and placebo separately in ET and AT patients, and in Schizophrenia patients:

Table 4.8.1.1. Rate of Mortality Observed

	Deaths	N	PYs	Rate / 100 PYs	RR** 95% CIs
Completed Trials					
ET Patients					
Pramipexole	1	416	139.64	0.72	0.80 (0.051, 12.65)
Placebo	1	262	111.61	0.90	
AT Patients					
Pramipexole	3	286	119.14	2.52	2.874 (0.303, 27.23)
Placebo	1	289	113.94	0.88	
Schizophrenia					
Pramipexole	0	117	15.59	0.0	
Placebo	0	95	9.22	0.0	
Completed and Open-Label Ongoing Trials					
ET Patients					
Pramipexole	4	675	363.12	0.11	not applicable#
Placebo	1	262	111.61	0.9	
AT Patients					
Pramipexole	8	556	436.30	1.83	not applicable#
Placebo	1	289	113.94	0.88	
Schizophrenia					
Pramipexole	0	117	15.59	0.0	
Placebo	0	95	9.22	0.0	

** Rate Ratio (Relative Risk) of Pramipexole is defined as: (Death/PYs of PPX)/ (Death/PYs of Placebo)

Because all patients in the ongoing part received pramipexole.

Three patients in study 0012 died but are not included in this table because the randomization codes, # of patients, and drug exposure data were not available. Among these patients, two (#23 and 424) received PPX (and died more than 30 days after the day of the last dose), one (#118) received placebo.

In the completed ET trials, the 6-month mortality risk was 0.24 per 100 patients (1/416) for pramipexole and 0.38 (1/262) for placebo. In the completed AT trials, the 6-month mortality risk was 1.1 per 100 patients (3/286) for pramipexole and 0.4 per 100 patients (1/289) for placebo.

The pramipexole mortality rate per 100 PYs was 3.5 fold greater in AT compared to ET pramipexole exposed patients, but equivalent in the placebo patients. In either ET or AT patients, pramipexole mortality was less than that observed with ropinirole (see Ropinirole NDA review; in a recent publication[2] describing mortality of the Honolulu Heart Study cohort, the mortality rate in year olds who developed PD was about 5 per 100 PYs.)

There were no deaths reported in the schizophrenia and depression (completed or ongoing) studies. There were no deaths reported in the 19 Phase 1 studies.

4.8.2 Description of Deaths Observed During Pramipexole's Use

Of the 14 pramipexole deaths, 8 were potentially CV in nature. These 8 deaths are summarized below.

Patient 2433 was a 72YOM who entered the ET study 0001. Parkinson's Disease had been diagnosed 6 months previously. The patient's medical history included coronary artery disease (CAD), myocardial infarction (MI) and triple coronary artery bypass graft surgery (CABG) in 1991, and congestive heart failure (CHF) with resultant liver disease. At baseline, the patient's vital signs were normal. His baseline ECG showed first-degree heart block, left atrial pathology, an old inferior myocardial infarction, poor R-wave progression, and nonspecific ST-T wave changes. The baseline chest X-ray showed moderate cardiomegaly, minimal scarring in the left lung, and emphysematous changes in the upper lobes. During the study, the patient concomitantly received hydrochlorothiazide and lisinopril. The patient was receiving pramipexole 3 mg per day when, on day 29, he experienced mild nausea, which he attributed to an empty stomach. The investigator considered this to be possibly

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[2] 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.

follow-up telephone call by study staff that evening, the patient stated that the nausea had resolved. On day 32, the patient had an MI and died. The investigator considered these medical events to be unrelated to study medication. Autopsy revealed cause of death to be an MI.

Patient 1065 was a 72YOM who entered the AT study 0010. He had a 5 year history of PD. The patient was maintained on carbidopa-levodopa. Past medical history was significant for an asymptomatic chronic aortic valve murmur with aortic stenosis since 1988, and drug allergies to penicillin and erythromycin. The patient had never smoked and consumed an average amount of ethanol. On dosing day 29 (pramipexole 3.0 mg/day) the patient complained of shortness of breath. The patient was admitted to the hospital and diagnosed with severe pneumonia and severe CHF. While in the hospital, the patient was treated with erythromycin as well as other antibiotics for the pneumonia. He was also given furosemide for CHF. After 7 weeks in the hospital, the pneumonia apparently resolved. The patient was then discharged from the hospital and transferred to a rehabilitation center. After 4 days the patient's condition deteriorated and he was admitted to the coronary intensive care unit. A doppler was done and it indicated destruction of 2 heart valves. The patient died. The patient's wife stated that he died of pulmonary edema (CHF). The investigator indicated neither was related to study drug. The cause of death was coded as CHF.

Patient 1021 was a 64YOM who entered the AT study 0010. He had a 12 year history of PD who began study medication on 10/5/93. Past medical history included dementia, hallucinations, leg cramps, and lightheadedness with an unknown onset date. The initial ECG at study entry showed normal sinus rhythm without evidence of a past infarct. Medication at entry included carbidopa-levodopa 50/200 and amantadine. The patient was an ex-smoker who had not consumed ethanol. At Visit 16, the patient had an ECG per protocol which showed an old inferoposterior wall MI with laboratory results showing a CPK level of and AST (SGOT) at . The MB fraction of the CPK was elevated at The patient apparently had an asymptomatic infarct some time prior to this study visit. In the morning the patient was found dead at home by his wife. The investigator felt that the patient had an infarct of severe intensity as the cause of death although there was no autopsy performed.

Patient 2227 was a 71YOM who entered the ET study 0001 followed by the open-label phase of the study (0002). He was diagnosed with PD 2 years prior to entry in the double-blind phase. The patient's relevant medical history included hypertension, which started 2 years prior to entry in the double-blind phase. During the study, he concomitantly received L-deprenyl 10 mg per day. During the maintenance-dose interval of the double-blind phase, he received pramipexole 2.25 mg per day. In the open-label phase, he completed the ascending-dose interval and entered the maintenance-dose interval receiving pramipexole 0.75 mg per day. The patient's clinic visit on day 60 was unremarkable. The following day (day 61), the patient

went for a walk and subsequently died at home from a possible pulmonary embolism (PE). There were no precipitating adverse events. The investigator considered the PE to be unrelated to the study medication. There was no autopsy performed to document the occurrence of PE.

Patient 2441 was s 80YOM who entered the ET study 0001 followed by the open-label phase of the study (protocol 0002). He was diagnosed with PD 4 years prior to entry in the double-blind phase. The patient's relevant medical history included angina pectoris, CAD, and bypass surgery (all 14 years prior to entry in the double-blind phase), hyperlipidemia (9 years), and shortness of breath and lightheadedness of unknown etiology (1 year). At the first study visit, the patient's ECG showed minimal voltage of LVH, possibly due to an inferior infarct approximately 3 years prior to entry in the double-blind period, and occasional ventricular complexes. He received no concomitant medications for PD during the study. He completed the ascending-dose interval of the open-label phase and entered the maintenance-dose interval receiving pramipexole 4.5 mg per day. On day 126 the patient was hospitalized because of severe chest pain. Prior to admission to the hospital, the patient had taken nitroglycerin sublingually and his symptoms had resolved. Results of an ECG showed atrial fibrillation. The patient was treated with diltiazem (bolus and IV drip) and normal sinus rhythm was restored. His CPK values remained normal , and CK-MB was . He was discharged from the hospital on day 129. The following day (day 130), the patient collapsed and died. The cause of death was reported as probably a massive M.I. The chest pain, atrial fibrillation, and M.I. were considered by the investigator to be unrelated to the study medication.

Patient 36 was a 65YOM who entered the AT open-label/ongoing study 0014. He had PD for a duration of 21 years which was treated with levodopa/decarboxylase inhibitor and biperiden. Patient history included mild cardiac insufficiency, and swallowing difficulties. He was also receiving hydrochlorothiazide/amiloride for cardiac insufficiency, and trimethoprim/sulfamethoxazole, and acetylcysteine for bronchitis. The patient was receiving pramipexole 4.0 mg/day and levodopa/benserazide, and biperiden. The patient suffered from dyspnea on 12/20/93 which was suspected to be related to a mild cardiac failure: this was treated with furosemide and then amelioride. The episodes of dyspnea reappeared. A lung embolism was suspected but not confirmed on a pulmonary scintigraphy. A relapsing bronchitis possibly due to aspiration because of Parkinson's disease-related swallowing difficulties was diagnosed. The patient was hospitalized from 8/16/94 to 8/20/94 and the diuretic discontinued. On 8/11/94 recurrent syncopes occurred, sometimes obviously following episodes of dyspnea. The neurologist interpreted these syncopes as most probable of the pressor-postpressor type. As a consequence of these events, the daily dose of pramipexole was reduced from 4.0 to 3.0 mg/day by the patient. The patient died on 9/1/94 following syncope. The family doctor stated cardiovascular arrest was the cause death. No autopsy was performed.

Patient 23 was a 75YOM who entered the AT ongoing study 0012. Patient history included posterior M.I., multiple bypass surgery, pulmonary emphysema, extra heart beats, and left anterior hemiblock. Concomitant medications included dihydroergotamine mesylate for low blood pressure, triamterene/hydrochlorothiazide for edema, and acetylsalicylic acid for the condition following the bypass surgery. Pramipeoxle was reduced from 2.25 mg/day to 0.75 mg/day from 10/20/94 to 10/31/94 due to moderate visual hallucinations. He had extra heartbeats on 10/22/94 which were treated with potassium. On 11/9/94 he had moderate dyspnea. Pramipexole was increased again to 2.25 mg/day on 11/10/94. Severe global heart insufficiency was reported on 11/20/94 and required patient hospitalization on 11/25/94. Torasemide treatment began on 11/22/94 and Dihydroergotamine Retard® and Isoptin 80® (verapamil) were discontinued. Study medication was discontinued. He was discharged from the hospital. He died at home of unknown cause. The investigator assessed that there is no reasonable possibility that the global heart insufficiency was caused by the study drug.

Patient 424 was a 76YOM who entered the AT ongoing study 0012. He had Parkinson's disease since 1985. Patient history included acute M.I. and ischemic heart disease. The patient was a known asthmatic for 10 years on chronic bronchodilator therapy. The patient was admitted to the hospital due to shortness of breath on 7/29/94. The patient was diagnosed with hyper-inflated chest with wheezes and breathlessness due to acute infective exacerbation of asthma. Pramipexole was discontinued. The patient was treated with bronchodilators, prednisolone, and erythromycin and was discharged. The patient was readmitted to the hospital with acute breathlessness. The patient was diagnosed with left ventricular failure secondary to ischemic heart disease and exacerbated chest infection. The patient's condition deteriorated with evidence of heart failure and he died. The cause of death was chronic obstructive airway disease with left ventricular failure. Although there was no autopsy to confirm.

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4.9 All-Cause and AE Dropout Risks

4.9.1 ET Studies

Table 4.9.1.1 shows the reasons for study dropout in ET patients (completed double-blind placebo-controlled PD trials) by treatment groups.

Table 4.9.1.1 Premature discontinuations: ET Trials (1, 4, & 21)

Reason For Discontinuation	Number (%) of Patients			
	Pramipexole (N=388)		Placebo (N=235)	
	N	%	N	%
Adverse Events	46	11.9	25	10.6
Lack of efficacy	1	0.3	8	3.4
Protocol Violation	1	0.3	0	0
Lost to Follow-up	3	0.8	0	0
Other	5	1.3	5	2.1
Total Patients	56	14.4	38	16.2

Using a data cutoff date of 1/31/95, the all-cause dropout risk was 14.4% (56/388) in pramipexole ET patients compared to 16.2% (38/235) in placebo.

There were differences in reasons for dropout by treatment group. The AE dropout risk was 11.9% with pramipexole (46 patients) compared to 10.6% with placebo (25 patients). A larger percentage of patients was withdrawn from study because of lost to follow-up with pramipexole than placebo and the opposite was the case for lack of efficacy.

The all-cause dropout risk and AE dropout risk associated with pramipexole use was variable across ET studies. In study 1, the all-cause dropout risk was 17% (28/164) for pramipexole and 20% (34/171) for placebo treated patients. In pramipexole treated patients, the AE dropout risk was 13% (22/164) compared to 14% (24/171) with placebo. In study 21, the all-cause dropout risk was 18% (2/11) for pramipexole and 23% (3/13) for placebo treated patients, and these dropouts were due to AEs.

In study 4, the all-cause dropout risk was 6 times greater with pramipexole, 12% (25/213) than with placebo 2% (1/51). This difference was mostly due to a difference in dropouts associated with AEs. In pramipexole treated patients, the AE dropout risk was 10% (22/213) compared to 0% (0/51) with placebo. This

difference in AE dropout risk seeems to be due to the fact that study 4, as mentioned earlier was a dose-response tolerability study and reached doses of 6.0 mg/day in one of its arms. Clinical intolerance occurred more at this highest dose, whereas in the other protocols the maximum dose reached was 4.5 mg/day.

The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

4.9.2 AT Studies

Table 4.9.2.1 shows the reasons for study dropout in AT patients (completed double-blind, placebo-controlled PD trials) by treatment groups.

Table 4.9.2.1 Premature discontinuations: AT Trials (10, 19, 20, & 22)

Reason For Discontinuation	Number (%) of Patients			
	Pramipexole (N=260)		Placebo (N=265)	
	N	%	N	%
Adverse Events	30	11.5	42	15.8
Lack of efficacy	0	0	1	0.4
Protocol Violation	1	0.4	2	0.8
Lost to Follow-up	0	0	2	0.87
Other	9	3.5	7	2.6
Total Patients	40	15.4	54	20.4

The all-cause dropout risk was 15.4% (40/260) in pramipexole AT patients compared to 20.4% (54/265) in placebo.

The AE dropout risk was 11.5% with pramipexole (30 patients) compared to 15.8% with placebo (42 patients).

The clinical characteristics of the AEs associated with dropout are discussed in section 4.10.

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4.10 Clinical Characteristics of AEs that were Associated with Dropout

Across all phase 2/3 studies, 127 pramipexole patients dropped out of study associated with a serious AE occurrence. No separate lists were provided for the dropouts due to serious AEs for the ET patients and AT patients. Appendix 4.11.1 provides a listing of all serious AEs associated with dropout across all studies. These events were reviewed using the narrative summaries and other supporting data. Overall, there were no cases of agranulocytosis, aplastic anemia, serious skin reactions such as Stevens-Johnson Syndrome, hepatic failure or necrosis, and renal failure or worsening of renal function that were associated with dropout. One patient was discontinued for immune thrombocytopenia and 3 more because of elevated CPKs, with one patient experiencing rhabdomyolysis. Cases are discussed in 4.11 along with other serious 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 pramipexole was 2.1% (8/388), while 1.3% (3/235) using placebo. Based upon a review of the investigator verbatims of the 8 patients with serious AEs associated with pramipexole dropout in ET patients, 1 had an AE that was cardiovascular in nature, and this patient eventually expired, (this patient# 2433, study 1 is summarized in the mortality section 4.8.2). The 7 remaining patients were recorded under investigator verbatims of drowsiness (associated with an MVA), decreased platelets, abdominal pain, somnolence (ran off the road in car), paranoid psychosis, sensory hallucinations, and confusion/hallucination.

4.10.1.2 Most Common AEs associated with Dropout in ET Patients

Table 4.10.1.2.1 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% of patients:

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Table 4.10.1.2.1

ET Patients

Adverse Events Which Caused Study Termination

Occurring with Frequency >= 1%

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	388	235
CONFUS	4 (1.03)	0 (0.00)
DIZZINESS	8 (2.06)	2 (0.85)
EXTRAPYR SYND	6 (1.55)	15 (6.38)
HALLUCIN	12 (3.09)	1 (0.43)
HEADACHE	5 (1.29)	0 (0.00)
NAUSEA	8 (2.06)	1 (0.43)
SOMNOLENCE	6 (1.55)	0 (0.00)

Studies included M/2730/0001, M/2730/0004, and M/2730/0021

Hallucinations, nausea, dizziness, somnolence, EPS, headache, and confusion were the only AEs associated with dropout in more than 1% of pramipexole patients. They also occurred at least 2 times more frequently than with placebo. Based upon our review of all dropouts from studies 1, 4, and 21, only 1 patient (patient 182, pramipexole exposed) dropped out due to syncope (0.3%).

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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

The serious AE dropout risk in AT patients using pramipexole was 3.1% (8/259), while 2.3% (6/266) using placebo. Based upon a review the investigator verbatims of the 8 patients with serious AEs associated with pramipexole dropout in AT patients, 2 had AEs that were cardiovascular in nature (patient #s 1021 and 1065) and both were discussed in the mortality section 4.8.2.

4.10.2.2 Most Common AEs associated with Dropout in AT Patients

Table 4.10.2.2.1 lists the AEs, irrespective of severity, that were associated with dropout in more than 1% of AT patients:

Table 4.10.2.2.1
AT Patients
Adverse Events Which Caused Study Termination
Occurring with Frequency >= 1%

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	260	264
CONFUS	3 (1.15)	6 (2.27)
DIZZINESS	3 (1.15)	4 (1.52)
DYSKINESIA	5 (1.92)	2 (0.76)
EXTRAPYR SYND	4 (1.54)	13 (4.92)
HALLUCIN	7 (2.69)	1 (0.38)
HYPOTENS POST	6 (2.31)	3 (1.14)

Studies included M/2730/0010, M/2730/0019, M/2730/0020, and M/2730/0022

Hallucinations, dyskinesia, and postural hypotension were associated with dropout in more than 1% of pramipexole patients and occurred 2 times more frequently than with placebo. No pramipexole patients dropped out because of syncope, while 3 patients (#s 1399, 1411, and 1302) dropped out because of syncope, all from protocol 10.

4.11 Serious AEs Associated with Pramipexole

In the ISS, serious AE risks were not described separately for ET and AT patients, as noted earlier a separate analysis was performed for this review. In the 3 ET RCTs the serious AE risk was 5.1% (20/388) with pramipexole and 5.5% (13/235) with placebo. Of these 20 pramipexole patients with serious AEs, 7 were CV in nature. One of these 7 was discussed in the mortality section, of the remaining 6, 2 were MIs, 2 were angina pectoris, and 1 each of pulmonary embolism and left ventricular dysfunction (reported as dyspnea).

Seven of the remaining 13 patients with serious non-CV AEs in the ET studies, were described under section 4.10.1.1. Of the remaining 6 patients, 2 had prostate cancer and 1 patient each were reported to have the following: fractured hip, thyroid nodule, basal cell carcinoma, and early rectal cancer.

In the 4 AT RCTs, the serious AE risk was 7% (18/259) with pramipexole and 7.5% (20/266) in placebo. Of the 18 patients with serious AEs, 3 were CV in nature, of which 2 have been discussed in section 4.8.2, and the other (patient 30, study 19) was reported to suffer from angina pectoris and stenocardia. The remaining 15 patients were reported to have the following: pneumonia, dyskinesia, fractures, somnolence, bladder cancer, paranoia, nausea, neck pain, CPK elevation, increase of periods, back pain, abdominal pain, confusion, and multiple myeloma.

The patients coded with dyspnea had other ongoing AEs such as CHF or pneumonia.

Appendix 4.11.1 provides a listing of all serious AEs occurring in pramipexole and placebo patients. There were no serious AEs consistent with liver failure or necrosis, agranulocytosis, aplastic anemia, hemolytic anemia, or seizures. Several cases are worth summarizing for their possible association with the study medication.

Cardiovascular

In ongoing study #0036, patient #663 experienced severe orthostatic hypotension after the initial dose of pramipexole. This patient was a 72 YOWM (with a history of PD diagnosed in 1994 and treated with selegiline and levodopa-carbidopa. Concomitant medications were numerous and included: estrogen, Cyproterone, entrophen for prostatic CA, lactulose for constipation and phenazo-pyridine and lorazepam. He did not smoke. The patient received one dose of pramipexole (0.125mg). One hour following initial dose, the patient was reported to have experienced what was termed "severe orthostatic hypotension", with symptoms characterized by feeling faint and lightheadedness. He appeared pale with a rapid pulse. The supine blood pressure was and the standing blood pressure was reported to be essentially 0. The patient was unable to stand for 3.5 hours post-dosing. When able to stand, his standing blood pressure was The ECG reading was reported to be normal. The patient was admitted to

the hospital for overnight observation, bedrest and IV fluids. The next day the patient was discharged but complained of lightheadedness and dizziness. Study medication was discontinued following the first dose. Incidentally, the patient had no previous history of symptomatic orthostatic hypotension. At baseline his supine vital signs were upon standing they were The investigator indicated that the event was probably related to study medication.

Hematologic

Patient #130 (protocol 0004) discontinued on study day 47 because of severe (life threatening) thrombocytopenia. The baseline platelet count was cells/mm^3; on day 40 the count was /mm^3. This was a 72 year old male who was on a 4.5mg per day of pramipexole. The narrative summary and CRF (Volume 576) of the patient revealed that this was a patient who had Parkinson's disease diagnosed approximately 4 years previously. This patient had a past medical history of hypertension (since 1994) and received nifedipine during the study. He began treatment with nifedipine 216 days prior to study entry. On day 40 as mentioned previously the platelet count had decreased significantly. The hemoglobin value and WBC count were unchanged from baseline. On day 43, repeat laboratory results showed a platelet count of cells/mm^3. The patient was discontinued from the study. On day 47 the platelet count was cell/mm^3. On day 55 bone marrow aspiration showed a slight hypercellularity and trilineal hyperplasia, indicating no bone marrow suppression. The patient was followed by a hematologist. The investigator considered the decreased platelet count to be possibly related to study medication and/or nifedipine. No further information is available on this patient.

Respiratory

Patient #30 (study 0004) was a 77 YOM with pre-existing heart disease and left ventricular dysfunction. The patient had a history of hypertension and coronary arteriosclerosis since 1987 and had cardiac bypass surgery in 1988. During this study, he concomitantly received nifedipine and acetylsalicylic acid and deprenyl for Parkinson's disease. At baseline his vital signs and ECG were normal. On day 8, he began reporting moderate edema in his left ankle but no cardiac symptoms. The patient was receiving 3mg/day of pramipexole when on day 32 he began having dyspnea. On day 36 while receiving 4.5mg/per day of pramipexole the patient was hospitalized because of continued dyspnea. He was found to have pulmonary congestion and ventricular dysfunction. He was discontinued from the study. On day 50, he underwent cardiac bypass surgery. On day 99, the patient was discharged from the hospital.

Serious Laboratory Abnormalities

Patient 1092 was a 49 YOWM ( ) with a 5 year history of Parkinson's (carbidopa-levodopa Rx) on multiple medications. Patient had episodes of dizziness, lightheadedness, dyspnea and pain in neck, back and chest for 4 days (7/12/93) prior to a blood pressure reading on 7/16/93 which revealed asymptomatic hypotension (supine vs = and standing vs =) compared with baseline readings of: for supine and) for standing. Seven days (7/23/93) after the orthostatic hypotension at the next laboratory determination an increase in CPK was noted and he was hospitalized diagnosed and treated for rhabdomyolysis. He had a marked increase in CPK-). The CPK was fractionated and found to be His baseline on 6/25/93 was Patient also had other abnormal laboratory results reflecting release of intracellular contents from skeletal muscle injury, e.g., LDH, AST and uric acid (escaped muscle purine catabolism). His CPKs decreased when drug was stopped. The narrative summary contained in volume 102 stated that patient had multiple bruises. This information was not seen in the CRF.

4.12 AEs Associated with a Change in Pramipexole Dose

AEs that were associated with a reduction in pramipexole dose were similar to the pattern seen with discontinuations.

4.13 AE Risks Associated with Pramipexole Use Irrespective of Severity

4.13.1 Overall

4.13.1.1 ET Patients

Appendix 4.13.1.1.1 lists AEs that were reported in ≥1% of ET patients assigned pramipexole in placebo controlled ET studies.

Table 4.13.1.1.1 lists the AEs that were reported at twice the rate of placebo and ≥1% (the rest of the AEs in appendix 4.13.1.1.1 were comparable to or less frequent than placebo):

Table 4.13.1.1.1
ET Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	388	235
Fever	4 (1.03)	1 (0.4)
Nausea	107 (27.6)	42 (17.9)
Constipation	53 (13.7)	14 (6.0)
Anorexia	17 (4.4)	5 (2.1)
Dysphagia	7 (1.8)	1 (0.4)
Weight decrease	7 (1.8)	1 (0.4)
Somnolence	85 (21.9)	21 (8.9)
Insomnia	66 (17)	27 (11.5)
Hallucination	35 (9)	6(2.6)
Confusion	16 (4.1)	3 (1.3)
Amnesia	14 (3.6)	4 (1.7)
Hypesthesia	11 (2.8)	2 (0.9)
Akathisia	6 (1.5)	0
Thinking Abnormal	6 (1.5)	1 (0.4)
Libido Decreased	5 (1.3)	0
Myoclonus	5 (1.3)	1 (0.4)
Vision Abnormality	10 (2.6)	0 (0.00)

Studies included M/2730/0001, M/2730/0004, and M/2730/0021

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Somnolence (21.9%), constipation (13.7%), and hallucinations (9.0%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.13.1.2 AT Patients

Appendix 4.13.1.2.1 lists AEs that were reported in ≥1% of AT patients assigned pramipexole in placebo controlled AT studies.

Table 4.13.1.2.1 lists the AEs that were reported at twice the rate of placebo and ≥1% (the rest of the AEs in appendix 4.13.1.2.1 were comparable to or less frequent than placebo):

Table 4.13.1.2.1
AT Patients
Adverse Events Occurring Twice as Frequently as Placebo

Adverse Event	Number (%) of Patients	
	Pramipexole N(%)	Placebo N(%)
Total Patients (N)	260	264
Chest Pain	8 (3.1)	4 (1.5)
Dry Mouth	17 (6.5)	7 (2.7)
Peripheral Edema	6 (2.3)	2 (0.8)
CPK Increase	3 (1.2)	1 (0.4)
Twitching	6 (2.3)	0
Bursitis	4 (1.5)	1 (0.4)
Myasthenia	3 (1.2)	0
Dyskinesia	123 (47.3)	83 (31.5)
Hallucination	43 (16.5)	10(3.8)
Paranoid Reaction	5 (1.9)	1 (0.4)
Delusions	3 (1.2)	1 (0.4)
Sleep Disorder	3 (1.2)	0
Rhinitis	7 (2.7)	3 (1.3)
Pneumonia	5 (1.9)	0
Diplopia	3 (1.2)	0
Urinary Frequency	15 (5.8)	7 (2.7)
Vision Abnormality	8 (3.1)	2 (0.8)

Studies included M/2730/0010, M/2730/0019, M/2730/0020 and M/2730/0022

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Hallucinations (16.5%), urinary frequency (5.8%), and dry mouth (6.5%) were reported in at least 5% of pramipexole patients and were twice as frequent as with placebo.

4.13.2 Dose Response

4.13.2.1 Dose Response in ET Patients

Appendix 4.13.2.1.1 shows the effect of dose on AE risk for AEs that were reported in at least 10% of ET patients using pramipexole (irrespective of frequency in placebo). The sponsor's analysis was broken down not by individual doses but by phases: ascending, maintenance, and taper phases of the dosing cycles. The largest risk reported was during the ascending phase of the dosing. AEs shown are: asthenia, headache, infection, pain, constipation, nausea, dizziness, insomnia, and somnolence.

Since study 4 was designed as a specific dose response study, its dose-relatedness of adverse events was assessed separately. This study was performed in 264 patients with early Parkinson's disease. In this study patients were randomized equally to target dosages of 0, which was a placebo, 1.5mg; 3.0mg; 4.5mg or 6.0mg per day of pramipexole. (Doses given orally on a t.i.d. schedule with a six week dose escalation period and a four week maintenance period). With increasing dosages of pramipexole, there were more adverse events reported in the digestive system (nausea 15% (8/54), 17% (9/54), and 20% (11/55) for the 1.5 mg/day, 4.5mg/day, and 6.0mg/day doses, respectively) and the CNS (somnolence and insomnia) in the maintenance phase of the study. Vital signs were measured at each visit and time of last dose recorded, but the BP measurements were not timed to last dose.

4.13.2.2 Dose Response in AT Patients

Appendix 4.13.2.2.1 shows the effect of dose on selected AEs in AT patients following a similar approach as in ET patients. The sponsor's analysis was broken down not by individual doses but by phases: ascending, maintenance, and taper phases of the dosing cycles. The largest risk reported, here as well was during the ascending phase of the dosing. The AEs shown include dyskinesia, nausea, orthostatic hypotension, confusion, and hallucination.

No specific dose-response design studies were performed in the AT patients.

4.13.3 AE Occurrence and Plasma Concentration

Pramipexole plasma concentration was not measured at the time of AE occurrence in either ET or AT patients.

4.13.4 AE Risk by Time Since First Exposure

Appendix 4.13.4.1 shows risks for AEs reported in ≥ 10% of ET patient by time since first exposure.

Appendix 4.13.4.2 shows risks for AEs reported in ≥ 10% of AT patients by time since first exposure.

In general, the findings agree with those observed for dose response. The most frequently reported AEs, here as well occurred with the lower doses, which correspond with the ascending phase of the dosing.

4.13.5 AE Risk and Concurrent Medication Use

The sponsor examined the effect of concurrently used medications on AE risk that might be attributable to pramipexole 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 use 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.

4.13.5.1 AE Risk and Concurrent Medication Use In ET Patients

When examining the RRs (pramipexole compared to placebo), there were no differences of any consequence observed in the AE occurrence between the different concurrent medications analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.13.5.2 AE Risk and Concurrent Medication Use In AT Patients

When examining the RRs (pramipexole compared to placebo), there were no differences of any consequence observed in the AE occurrence between the different concurrent medications analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.13.6 AE Risk by Age, Gender and Race

Data from the pivotal trials were pooled in the ISS. For this review a subgroup analysis of AE risk by age and gender for the ET and AT trials was performed. Appendices 4.13.6.1-2 and 4.13.6.3-4 display the age (< 45, , and >75) and gender based analyses for AEs reported with a frequency of > 5% with analyses of relative risk (RR-relative rate for pramipexole/rate of placebo). A summary of findings in the appendices follows:

In the age analysis of the ET patients, when examining the RRs (pramipexole compared to placebo), there were no major differences observed in the AE occurrence between the different age groups analyzed. A search did not identify an RR that was two-fold greater than any comparison. However, there was a specific pattern of increasing RR with increasing age for the reported AE Hallucination.

In the age analysis of the AT patients, when examining the RRs (pramipexole compared to placebo), there were no major differences observed in the AE occurrence between the different age groups analyzed. A search did not identify an RR that was two-fold greater than any comparison. However, there was a specific pattern of increasing RR with increasing age for the reported AE Hallucination (even more prominent than with the ET patients).

In the gender analysis of the ET patients, depression was reported at a > two-fold higher RR in males than in females; and hallucination was reported at a > two-fold higher RR in females than in males. Other AEs were comparable.

In the gender analysis of the AT patients, dyspepsia was reported at a > two-fold higher RR in males than in females; and hallucination and urinary frequency were reported at a > two-fold higher RR in females than in males. Other AEs were comparable.

There were too few non-white patients exposed to pramipexole to examine variation in risk by race.

4.13.7 AE Risk for Selected Underlying Diseases

To describe any potential modification in pramipexole risk for patients with selected underlying (concurrent) diseases, The sponsor used a similar approach to that with concurrently used medications and for demographic subgroups. Concurrent disease was defined as illness present at baseline. Concurrent diseases that occurred in >=5% of pramipexole patients were used to calculate the relative risk. The concurrent diseases selected for study were arthritis, CV disease, constipation, depression, dizziness, hypercholesterolemia, hypertension, insomnia, and prostate disease.

When examining the RRs (pramipexole compared to placebo) in ET patients, there were no differences of any consequence observed in the AE occurrence between the different concurrent illnesses analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

When examining the RRs (pramipexole compared to placebo) in AT patients, there were no differences of any consequence observed in the AE occurrence between the different concurrent illnesses analyzed. A search did not identify an RR that was two-fold greater than any comparison. Overall, no specific patterns were noted.

4.14 AE Risk During Tapering

There were no significant differences in the AEs reported during tapering. In protocols where dose reduction was followed, no AEs could be attrbuted to drug withdrawal. There seemed to be more AEs (tremor, EPS, and hypokinesia) consistent with worsening of PD.

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4.15 Changes in Laboratory Parameters Associated with Pramipexole Use

Here again, the sponsor primarily presented pooled analysis of the "adequate and well-controlled studies", 0001, 0004 (the studies in early PD patients) and 0010 (the study in advanced PD patients), without disregarding the other 6 PD studies. This portion of the review will follow the sponsor's approach. However, it should be noted that the individual ET and AT study reports were reviewed. Appendix 4.15.1 displays the laboratory criteria used by the sponsor as normal values; values outside these predefined limits were flagged. Appendix 4.15.2 summarizes the data of laboratory values with abnormal shifts (outside these predefined limits) in the 3 pivotal trials.

Hematology

Except for lymphocytes, the incidence of hematologic laboratory values exceeding predefined limits for pramipexole-treated patients was less than that of placebo patients and/or was lower than 1%. Approximately 3% of the pramipexole-treated patients (16/547) vs approximately 2% of placebo-treated patients (7/394) had lymphocyte values lower than the predefined limits. There was no statistically significant differences between the groups (Sponsor's Fishers' Exact Test, p=0.292).

There were no statistically significant changes in mean hematologic values for the pramipexole and placebo groups separately and when compared to each other across the baseline values. There was no evidence of dose-relatedness (1.5mg/day to 6.0mg/day in protocol 0004) for the hematologic analytes measured: HgB, WBC, and platelets.

For the other PD studies there were 2 pramipexole-treated patients (1.5%) who had spurious low lymphocyte values outside the predefined limits during treatment compared with 3 (2.2%) of the 137 placebo-treated patients.

In the PD studies one patient (patient #130, protocol 0004) out of 702 of the pramipexole-treated patients discontinued due to thrombocytopenia (case discussed in section 4.11). One placebo-treated patient (0.3%) discontinued because of leukopenia. In the completed schizophrenia studies, as well as the ongoing studies in Parkinson's disease, there were no reports of discontinuations because of hematologic laboratory values. In the review of deaths and serious AEs, no cases of aplastic anemia or agranulocytosis were found.

Blood Chemistry Parameters

Appendix table 4.15.2 summarizes all patients with laboratory data exceeding predefined limits in the pooled adequate and well-controlled studies. The proportion of patients which moved from a predefined normal GGT and CPK value to a higher abnormal value were 2% and 3.5%, respectively, in the pramipexole treated patients. These shifts were similar in the placebo treated patients. About 1% of the pramipexole treated patients had shifts to

abnormal values for AST and ALT. This was not observed for placebo. The incidence of shifts in other analytes (both for placebo and pramipexole treated patients) were less than 1% and clinically not significant.

A summary of patients with elevated CPKs is located in Appendix table 4.15.3. It enables one to appreciate the wide range of dispersion in values for both treatment groups. In the pooled database 19 (3.5%) of the pramipexole treated patients compared with 9 (2.3%) of the placebo treated patients had CPK values which exceeded predefined limits. There was no statistically significant difference between the two groups, (sponsor's Fishers' Exact Test, $p=0.335$).

Of the 19 pramipexole treated patients with elevated CPKs, 13 were reported in the 2 early Parkinson's studies and 6 in the advanced Parkinson's study 0010. In the placebo group, there were 5 reports in the early and 4 reports in the advanced. The AT study 0010, reported a statistically significant mean change elevation from baseline in total CPKs in the pramipexole group compared to the placebo group (+21.31 vs -1.28, $p<0.003$). The ET dose-response study (protocol 0004), also reported a mean change from baseline greater in the pramipexole than placebo group for both the ascending and maintenance phases at all doses other than the 4.5mg/day dose. Table 4.15.1, which displays the mean changes from baseline to endpoints for CPKs during the dosing periods for protocol 0001, can be considered representative of all PD studies:

Table 4.15.1. Mean changes from baseline to endpoints for CPKs

Group	WEEKS Ascending*		Maintenance		Reduction
	4	7	8	16	24
Pramipexole	+24	+27	+32	+31	+30
Placebo	+9.5	+1.0	+8.0	+6.0	+13

+ = Dosing phases

In the 6 studies designated other controlled studies, only the laboratory analyte CPK exceeded predefined limits (shifts to abnormal). Five (7%) of the 76 pramipexole patients exceeded predefined limits compared with none of the 83 placebo patients evaluated. For three of the five pramipexole patients, the abnormal values were spurious. For the other two patients their endpoint values remained elevated: one patient started with a high baseline CPK value of 257 u/L (normal range: u/L) and at endpoint it was 336 u/L. The remaining patient (No. 20, Protocol 0020) was a 58-year old man with a CPK value of 86 u/L at baseline, at day-22 value of 219, and an endpoint value (day 48) of 3498 u/L. The patient was discontinued because of this elevated CPK. Although the patient had many other adverse events, a cause for the elevated CPK could not be identified by the investigator. Myopathy was not reported. After drug discontinuation, the CPK had returned to within the normal range.

As discussed in previous sections (serious and dropouts), a careful assessment for rhabdomyolysis was performed (by examining individual CRFs) and one patient was found that experienced rhabdomyolysis. The case is discussed in the serious AEs section.

Patients with increased GGTs are summarized in Appendix table 4.15.3. Of the 11 patients with GGT values outside the predefined limits during treatment, 5 had baseline elevations and 6 had post baseline elevations. Four pramipexole treated patients, from protocol 10, (number 1061, 1118, 1171, and 1226) had GGT values which ranged from : u/L (NR: 0-65 u/L). In all cases patients had clinically significant elevations of other liver enzymes as well (either AST or ALT values). In the placebo group one patient (number 1242) was identified with clinically significant elevations in GGT (value was 268 u/L). Mean changes in GGT levels from baseline were examined and there were no statistically significant differences between pramipexole and placebo.

Four patients (#s 182, 1171, 1021, 1092) had elevated ASTs and 4 patients (#s 1171, 1061, 1226, 1118) had elevated ALTs. Data are summarized in appendix table 4.15.3. The following patients reported values which were >=2.5 x ULN: patient #171 in protocol 0010 (AST, ALT and GGT); patient #1118, (ALT and GGT) and patient #1226, (ALT and GGT).

In protocol 10 (AT trial), there were statistically significant mean change elevations of ALT and AST from baseline in the pramipexole treated patients. Table 4.15.2 displays these differences:

Table 4.15.2. ALT and AST mean change from baseline

		Mean change from Baseline		
Visit number	Laboratory analyte	Pramipexole	Placebo	p-value
18	ALT IU/L	+5.14	0.28	0.005
	AST IU/L	+2.43	0.02	0.02
19	ALT IU/L	+4.3	-0.9	0.001
	AST IU/L	+1.8	-0.7	0.01

There were no differences in mean changes from baseline to designated endpoints between the treatment groups with respect to AST and ALT values in protocols 1 or 4 (ET trials).

One patient in protocol 0010 (patient #1226, CRF in volume 610) withdrew from pramipexole treatment because of the adverse event hepatitis and abdominal pain. He had elevated hepatic enzymes and is discussed in this section. Patient #1226 was a 67-year old white male with a past medical history significant for a cholecystectomy, kidney stones and removal of skin cancer. The patient had Parkinson's disease since 1964 treated with

antiparkinsonian medication including benztropine emsylate and carbidopa-levodopa. When the patient was seen for visit 5, the liver tests were noted to be markedly elevated with GGT at u/L (upper norma u/L) as well as elevated AST, ALT, and alkaline phosphatase (values could not be read from the CRF). Repeat liver function test at visit 6 showed further increases in AST and LDH (once again, the values were illegible). The dose level of study medication was increased as per protocol to dose level 5. At visit 7, a general hepatitis A screen was reported to be positive. However, further workup indicated patient did not have active hepatitis (only past exposure). Further additional workup for hepatitis B and C was reported to be negative. At visit 8, additional LFTs were done demonstrating continuing elevations and these values were noted to be as follows: AST value on visit 8 was u/L ( ), ALT was u/L on visit 8 and GGT value on visit 8 was u/L). Study medication was discontinued. Patient was referred to a gastroenterologist who felt that the patient's elevated LFTs were drug-related. Within 30 days of discontinuing medication, normalization of LDH, AST and ALT occurred. Throughout the total time period that LFTs were elevated total bilirubin levels remained within the normal range. Based upon the patient's course and normalization of laboratory abnormalities following discontinuation of study drug, the abnormal LFTs appeared to be possibly related to the pramipexole. The patient did enter the open-label pramipexole study five months later. There were no reports of elevated LFTs.

As mentioned in the dropouts section, in the PD trials 3 pramipexole-treated patients and 1 placebo-treated patient discontinued because of chemistry AEs. These patients (pramipexole and placebo) discontinued because of increases in CPK, and were discussed earlier. In the completed schizophrenia studies, 1 out of 177 pramipexole-treated patients discontinued because of chemistry values considered abnormal (CPK increase--information on this patient is not available at this time) and 1 placebo-treated patient out of 95 discontinued due to an elevation in ALT. In the ongoing studies in Parkinson's disease, 1 out of 1,056 pramipexole-treated patients, discontinued (elevation in CPK). Patient #049 (protocol 0012 CRF in vol 667) discontinued because of increased CPK, pain in arm and back and dyskinesia.

Urine Analysis

Appendix table 4.15.2 lists the incidence of clinically significant urinalysis laboratory values exceeding predefined limits in the adequate and well-controlled studies. With the exception of urinary protein, the incidence of abnormalities for pramipexole-treated patients was less than that of placebo patients and/or was lower than 1%. In the pramipexole-treated patients 2.2% of the patients (8/364) vs 1% of the placebo-treated patients (2/219) had an abnormal laboratory urinary protein value which was abnormally high. Seven of the 8 pramipexole patients with urine protein values outside predefined limits also had protein in their urine at baseline.

There were no statistically significant changes in mean urinalysis analytes values for the pramipexole and placebo groups compared with baseline values.

In the other conrolled studies, the only value that was higher in the pramipexole-treated group compared to the placebo-treated group was the WBC in the urine where 25% of the pramipexole-treated patients (13/53) vs 10% of the placebo-treated patients (5/50) had values outside exceeding the predefined limits. There were no discontinuations reported.

There was no reporting in the ISS of urinary crystals. However, a review of numerous CRFs revealed that uric acid and calcium oxalate crystals were reported in pramipexole treated patients.

4.16 Changes in Vital Signs Associated with Pramipexole Use

Special attention was focused upon vital sign monitoring as a result of a clinical hold placed on the original IND because of reports of hypotension . In the phase 2/3 studies BP measurement was not timed relative to the time of dosing, but vital signs were checked at every visit.

As displayed in appendices 4.13.1.1.1 and 4.13.1.2.1, although there was little difference between pramipexole groups and placebo groups in the incidence of orthostatic hypotension, there was a great disparity between the ET and AT groups: 7.7% of ET patients taking pramipexole reported orthostatic hypotension and 52.7% of AT patients reported the same AE. A similar disparity between ET and AT placebo groups was noted.

A total of six (1%) of the pramipexole treated patients compared with 1 (0.3%) of the placebo treated patients discontinued treatment due to vital signs. Five (1 ET and 4 AT) of the six events were due to orthostatic hypotension.

4.17 Changes in ECG Parameters Associated with Pramipexole Use

Across the development program, there were no consistent changes in ECG or AEs that suggested that pramipexole had deleterious effects on cardiac function. Most studies had extensive ECG monitoring, and these did not reveal differences in incidence of any changes in ECG between pramipexole and placebo.

In the 3 adequate and well-controlled studies 0.5% (3/558) of the pramipexole treated patients compared with 0.2% (1/400) of placebo treated patients discontinued because of ECG abnormalities. Overall in the completed controlled studies in Parkinson's disease, 0.4% (3/702) of the pramipexole compared with 1% (4/551) of placebo treated patients discontinued because of ECG abnormalities.

The 3 pramipexole treated patients (patient numbers 114, 98 and 91) who discontinued from

protocol 0004 reported ECG abnormalities of palpitations, tachycardia, and an irregular heart rate (arrhythmia) that were not causally related to pramipexole. The 1 placebo patient (patient # 1399) was from protocol 10.

4.18 Dyskinesia

The Parkinson's Dyskinesia Scale (PDS) was used by investigators to characterize the severity of abnormal movements in patients. There was no difference in the PDS over time between treatment groups.

4.19 Review of Special Studies

4.19.1 Withdrawal Potential

Pramipexole is not a controlled substance. Pramipexole has not been systemically studied in animals or humans for its potential for abuse, tolerance or physical dependence; and receptor binding studies for the opiate receptors were not performed.

In protocols where dose reduction for one week was followed, no AEs could be attributed to drug withdrawal. Symptoms such as tremor, EPS, asthenia, hypertonia, gait abnormality, and hypokinesia during dose reduction were attributed to the underlying PD. In the clinical trials and in the labelling, the sponsor recommends that patients discontinue treatment gradually over a one-week period, despite instances of patients discontinuing abruptly or tapered at a rate faster than recommended exhibiting no withdrawal symptoms.

4.19.2 Interaction Studies

Four phase I studies were conducted to evaluate drug interactions of pramipexole with other drugs.

The potential interactions between probenecid, pramipexole, and cimetidine were investigated in six male and six female volunteers according to a three treatment crossover design (study 0061). This study demonstrated that concomitant therapy with drugs secreted by the cationic-transport system of the renal tubules may necessitate dose reduction of pramipexole.

In a modified and crossover design study (study 0063) of five male and four female volunteers, the pharmacokinetics of pramipexole and levodopa administration were examined. Pramipexole did not alter the extent of levodopa absorption, but there were differences in levodopa Cmax (42% increase) and Tmax (71% decrease) suggesting a faster rate of absorption, although the small number of subjects and the high degree of variability produced precluded a definitive estimate of the magnitude of this change. Titration of the levodopa dose to the individual patients optimum therapeutic response may be required

during concomitant treatment with pramipexole.

The sponsor did not perform drug metabolism studies. The rationale was that the high bioavailability (>90%) indicates no first pass effect and hence no phase 1 oxidative metabolism of the drug.

4.20 Human Reproduction Data

No pregnancy exposures were observed with pramipexole. Preclinical studies with high doses (1.5 mg/Kg/day) revealed embryo toxicity demonstrated by post-implantation loss, late embryonic deaths, and decreased fetal weights). No teratogenic effects were observed at any dose.

4.21 Human Carcinogenicity Potential

Pramipexole was not carcinogenic in the drug safety studies except for a 2 year study in rats, in which Leydig cell adenomas were found. The sponsor attributes the Leydig cell hyperplasia and increased number of adenomas to pramipexole-induced hypoprolactinemia. Because of the common occurrence of Leydig cell tumors in rats, the agency's cancer assessment committee (CAC) no longer requires mentioning of such tumors in the labelling.

4.22 Overdose Experience

There were no reports of intentional overdoses. There was only one report of an unintentional overdose in a patient with a 10-year history of schizophrenia. He took 11mg/day of pramipexole. No adverse events were reported.