

Table 1. Time and Events Table for Study 19.

Events	Screening	baseline	Titration period							Maintenance period		Dose reduction period
			1	2	3	4	5	6	7	8	9	
Visit ^{a)}	1	2	3	4	5	6	7	8	9	10	11	12
Week ^{a)}	week		end of week							end of week		week
	-3	-1	1	2	3	4	5	6	7	9	11	12
Informed consent	X											
Demographic data	X											
Medical history	X											
Neurological examination ^{c)}	X										X	
Inclusion/exclusion criteria		X										
Randomization		X										
UPDRS, Hoehn & Yahr, Schwab-New England		X	X	X	X	X	X	X	X	X	X	
Dyskinesia Scale		X	X	X	X	X	X	X	X	X	X	
Dispense of patient record	X									X		
Evaluation of patient record		X									X	
BP, pulse	X	X	X	X	X	X	X	X	X	X	X	X ^{b)}
Electrocardiogram ^{c)}	X	X ^{b)}			X		X ^{b)}		X		X	X ^{b)}
Laboratory tests ^{c)}	X	X ^{b)}			X		X ^{b)}		X		X	X ^{b)}
Dispensation of study medication		X	X	X	X	X	X	X	X	X	X	X
Dosage of concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Conclusion of participation - (Subs) Clinical Assessment ^{c)}											X	

- a) Visits in week -3, -1, 1, 2, 3, 4, 5, 6, 7, 9, 11 and 12 are mandatory if not otherwise stated.
 b) Only, if relevant changes at a previous visit compared to the screening/baseline value occurred.
 c) Investigations of week 11 should be performed at premature discontinuation.

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Table 2. Time and Events Table for Study 22.

SND 919: Time and events schedule of the study 838.008

Events	pre-treatment		treatment period							dose-reduction				
	1	2	dose-escalation				maintenance dose		10					
visit (a)	1	2	3	4	5	6	7	8	9	10				
	end of week		end of week				end of week		week					
week (a)	-3	-1	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	x													
Demographic data	x													
Physical examination c)	x											x		
Medical history	x													
Neurological examination	x													
Inclusion/exclusion criteria		x												
Telephone randomization		x												
UPDRS c)		x	x	x	x		x	x		x		x		
Fluctuations c)		x	x	x	x		x	x		x		x		
Dyskinesia Scale c)		x	x	x	x		x	x		x		x		
Patient record d)		1 week daily								1 week daily				
Adverse events c)	x	x	x	x	x		x	x		x		x		x
BP, pulse c)	x	x	x	x	x		x	x		x		x		x ^{b)}
Electrocardiogram c,f)	x	x ^{e)}					x ^{b)}	x		x		x		x ^{b)}
Routine laboratory investigations c)	x	x ^{e)}					x			x		x		x ^{b)}
Prolactin serum level g)	x	x ^{e)}					x			x		x		x ^{b)}
Delivery of the study medication		x	x	x	x		x	x		x		x		
Dosage of the concomitant medication	x	x	x	x	x		x	x		x		x		x
Global Clinical Impression c)		x										x		
Conclusion of participation c)												x		

- a) Visits in week -3, -1, 1, 2, 3, 5, 7, 9, 11 and 12 are mandatory if not otherwise stated.
- b) Only, if relevant changes occurred compared to the baseline value
- c) All investigation of week 11 should be performed also at premature discontinuation.
- d) Please, add to the case report forms a copy of the patient record of the reported "on" and "off" periods during waking hours and the severity of disability during "off" periods
- e) Repeat the investigation, if problems emerged at the 1st visit (Visit 2 = baseline).
- f) Please attach a copy of the ECG to the case record forms
- g) Blood will be drawn (6 - 7 ml) to determine prolactin serum levels

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Table 3.

Demographics Studies 19 and 22										
	Study 19				Study 22				Placebo	%
	SND 919 (Pramipexole)		Placebo		SND 919 (Pramipexole)		Placebo			
	No.	%	No.	%	No.	%	No.	%		
Total No. Of Patients Treated	34		44		36		33			
Male	20	58.82	31	70.45	20	55.56	20	60.60		
Female	14	41.18	13	29.55	16	44.44	13	39.39		
White	33		43		36		33			
Oriental	1		0							
Unknown	0		1							
Age (Years) Mean	59.3		60.66		63.2		62.1			
Weight (kg) Mean	71.86		73.99		69.7		71.0			
Duration of PD in Years Mean	7.80		8.49		10.1		9.9			
Hoehn & Yahr Stages										
II	7	20.58	13	29.54	15	41.67	10	30.30		
III	22	64.7	20	45.45	18	50	17	51.52		
IV	5	14.7	11	25	3	8.33	6	18.18		
Total Score of UPDRS Mea	53.60		50.24		51.9		56.7			
L-Dopa Treatment										
Other Anti-PD Medications										
Stratum 1 (600mg, no other meds)	5	14.71	7	15.91	14		11			
Stratum 2 (600mg, other meds)	15	44.12	16	36.36	22		22			
Stratum 3 (>600mg, no other meds)	4	11.76	8	18.18						
Stratum 4 (>600mg, other meds)	10	29.41	13	29.55						

Table 4.

	Supportive Efficacy Studies (19 and 22)														
	Study 19						Study 22								
	Pramipexole (N34)			Placebo (N44)			Pramipexole (N36)			Placebo (N33)					
ITT	Week	2	11	Diff.	Week	2	11	Diff.	Week	2	11	Diff.			
UPDRS - Total Mean Score (sum of I - IV)		53.7	33.6	20.1	50.2	44.4	5.9	16.9	51.9	35.0	16.9	16.9	56.7	47.7	9.0
UPDRS - I (mentation, behavior, mood)		1.5	0.8	0.7	1.1	1.2	-0.1	0.5	2.4	1.9	0.5	0.5	2.3	2.5	-0.2
UPDRS -II (activities of daily living)		13.0	8.6	4.4	12.7	11.7	1.1	3.4	13.4	9.9	3.4	3.4	14.9	14.2	0.7
UPDRS - III (motor exam.)		33.5	20.3	13.2	30.5	26.0	4.5	12.1	29.6	17.5	12.1	12.1	32.1	24.1	8.1
UPDRS - IV (complications)		5.7	3.9	1.8	5.9	5.5	0.4	1.0	6.6	5.6	1.0	1.0	7.4	7.0	0.4
Dyskinesia scale		2.70	2.12		3.70	2.77									
Evaluable (ITT - withdrawals, see table 7)		N29			N38			N30			N28				
UPDRS - Total Mean Score		52.3	29.7	22.6	47.4	41.2	6.2	18.7	50.9	32.2	18.7	18.7	57.1	46.2	10.9
UPDRS - I (mentation, behavior, mood)		1.4	0.8	0.6	0.9	1.1	-0.1	0.5	2.4	1.8	0.5	0.5	2.1	2.3	-0.2
UPDRS -II (activities of daily living)		12.7	7.7	5.0	11.8	10.5	1.3	3.7	12.7	9.0	3.7	3.7	14.9	14.0	0.9
UPDRS - III (motor exam.)		32.6	17.3	15.2	29.1	24.5	4.6	13.5	29.8	16.4	13.5	13.5	32.9	23.3	9.6
UPDRS - IV (complications)		5.7	3.9	1.8	5.6	5.1	0.5	1.0	6.1	5.1	1.0	1.0	7.2	6.7	0.5
Patient Record (% of waking off time)		32.97 (28)	20.69		32.7 2 (41)	34.6 1			32 (33)	26			43 (33)	40	
Mean Daily Dose		3.59 (29)			4.08 (38)			4.59 (32)			4.77 (21)				

Table 5.

Missing UPDRS Values*				
	Study 19		Study 22	
	Pramipexole	Placebo	Pramipexole	Placebo
Percent of Patients	16 (47%)	21 (47%)	17 (47%)	7 (21%)
From Visit 2 (Baseline)	1	2	2	2
From Visit 9 (week 11) (End of Maintenance Period)	2	2	11	6

* Includes patients that dropped out of the trial and patients with missing values from only part of the UPDRS i.e. Part IV item no. 39.

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Concomitant L-dopa Treatment						
Visit	Study 19			Study 22		
	Pramipexole		Placebo	Pramipexole		Placebo
	Mean (mg/d)	SD	Mean (mg/d)	SD	Mean (mg/d)	SD
From Visit 2 (Baseline)	537.5	314.4	592.6	264.0	727.8	339.8
From Visit 9 (week 11) (End of Maintenance Period)	511.0	308.8	583.5	273.3	577.1	340.9
					764.4	411.5

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Table 7.

Withdrawals (Adverse Events and Administrative) Studies 19 and 22				
	Pramipexole (N34) Baseline / Final Maintenance Visit	Placebo (N44) Baseline / Final Maintenance Visit	Pramipexole (N36) Baseline / Final Maintenance Visit	Placebo (N33) Baseline / Final Maintenance Visit
AE withdrawals	3 sedation / tiredness increased falls * drop BP / confusion drowsiness / myoclonia *during dose reduction period	5 nausea dizziness right bundle branch block felt inner restlessness influenza drowsiness dizziness arterial hypertension arterial hypertension (exclusion)	1 orthostatic hypotension	2 angina pectoris severe repetitive tachycardia
Admin. Withdrawals	1 withdrew consent	1 arterial hypertension	3 protocol violation withdrawal of consent lost to follow-up	1 protocol violation
Excluded due to treatment with increased amounts of anti- Parkinson's medications			2	
Patient enrolled twice first to placebo then to Pramipexole	1			

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Study 18

This was designed to be a **single-blind**, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 48 patients were to be enrolled.

Patients were advanced PD patients on L-dopa who experienced motor fluctuations. Concomitant anticholinergics were allowed. Concomitant amantadine was allowed. Deprenyl was not allowed.

There was a 7-week dose-escalation phase, with a maximal daily dose of 4.5 mg/day. Patients were titrated to maximal tolerated dose (MTD). If side effects developed during dose escalation, dose could be reduced to a prior tolerated dose and that patient would begin the maintenance phase. Following dose-escalation, there was a 3 week maintenance period and then a 1 week dose reduction period.

Replacement of dropouts was allowed (p 5 of the protocol).

"Patients who drop from the study prior to completing at least two weeks of the maintenance dose interval...or are less than 75% compliant with the study drug...will be replaced."

Assessments included Parts II of the UPDRS and patient diaries of on-off time. The primary outcome was a dual outcome: mean change from baseline on Part II of the UPDRS at the end of maintenance and percentage (and severity) of off time. The protocol never specified whether UPDRS Part II would be averaged for the primary analysis, or divided into separate outcomes for on and off scores.

Results:

Fifty patients were randomized (26 pramipexole; 24 placebo) at 6 centers in the United States.

The results for the evaluable, observed case analysis is shown below: ["Observed case" seems to be a misnomer here since, by protocol, if a patient had not been in the maintenance phase for 2 weeks, that pt was to be replaced.] One patient (1001) was considered unevaluable because the baseline L-dopa dose was exceeded during the study.

Adjusted Change From Baseline,UPDRS II"off"

Pramipexole	3.50 (n=24)	
Placebo	0.25 (n=20)	p=0.11

Adjusted Change From Baseline,UPDRS II"on"

Pramipexole	1.04 (n=24)	
Placebo	0.80 (n=20)	p=0.90

When maintenance scores were averaged over 3 weeks (as opposed to using only the final maintenance score) and then compared to baseline, a statistically significant difference seemed to emerge in favor of pramipexole by the sponsor's report.

The percentage off time did not differ between the two treatment groups.

A trend toward reduced severity of off time was noted.

No significant difference on UPDRS Part III was found.

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Conclusions:

There was a trend toward reduced severity of off time as measured by patient diaries and UPDRS Part II "off" scores. When maintenance scores were averaged over 3 weeks and then compared to baseline, a statistically significant difference seemed to emerge in favor of pramipexole.

On the other hand, the percentage off time did not change for either treatment group. Also, the UPDRS Part II "on" scores did not differ for the two treatment groups.

The maintenance period here was only 3 weeks long, making any extrapolation from these results difficult.

One aspect of this study that is important is the exclusion of deprenyl as a concomitant medication. It may be important from the standpoint of drug interactions that trends in favor of pramipexole were seen in the absence of deprenyl.

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Study 20

This was designed to be a double-blind, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. Because of slow enrollment, only 19 patients (9 pramipexole; 10 placebo) were enrolled. For that reason, no meaningful efficacy results emerged from this study in patients with advanced PD. According to the sponsor, "there were no apparent differences between treatment groups in the UPDRS or subscores."

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Conclusions:

The sponsor has demonstrated the effectiveness of pramipexole in early Parkinson's Disease in the absence of L-dopa. Additionally, effectiveness has been shown in advanced Parkinson's Disease with concomitant L-dopa therapy.

Studies in Early Parkinson's Disease

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Four studies are summarized in the two tables below. A consistent improvement in UPDRS Part II (the activities of daily living scale) is shown across studies.

Likewise, a consistent improvement in UPDRS Part III is shown across studies. UPDRS Part III is referred to as the motor scale. I would argue that the scale captures the motor exam minus the domain of involuntary movements (to include dyskinesias).

Early Parkinson's Disease; No Concomitant L-Dopa

Change From Baseline on UPDRS Part II:

	Study 1	Study 4	Study 17	Study 21
Pramipexole	1.9	1.8	5.2	5.1
Placebo	-0.4	0.3	2.2	2.2

Change From Baseline on UPDRS Part III:

	Study 1	Study 4	Study 17	Study 21
Pramipexole	5	4.5	12.0	7.2
Placebo	-0.8	0.6	8.3	1.6

Studies in Advanced Parkinson's Disease

Four studies are summarized in the two tables below.

Note that UPDRS Part II (ADL) in these studies represents an average score of the "on" score and the "off" score. As such, without a per patient correction factor for amount of "on" time and "off" time, it must be interpreted carefully.

A consistent improvement is shown across studies.

Likewise, a consistent improvement in UPDRS Part III (the motor scale) is shown across studies. Again, I would argue that the scale captures the motor exam minus the domain of involuntary movements (to include dyskinesias).

Advanced Parkinson's Disease; Concomitant L-Dopa

Change From Baseline on UPDRS Part II (average of on and off score):

	Study 10	Study 18	Study 19*	Study 22
Pramipexole	2.7	2.1	4.4	3.5
Placebo	0.5	0.5	1.0	0.7

Change From Baseline on UPDRS Part III:

	Study 10	Study 18	Study 19*	Study 22
Pramipexole	5.6	3.1	13.2	12.1
Placebo	2.8	1.4	4.5	8.0

* Study 19 is the only study in advanced PD where daily dosage of L-dopa was not differentially reduced in the pramipexole group as compared to the placebo group

Given the presence of the on-off phenomenon in patients with advanced Parkinson's Disease, the effect of pramipexole on total amount of "on" time is important to evaluate. As mentioned above, a positive effect here may even be a prerequisite for meaningful interpretation of the primary outcome, UPDRS Part II. Unfortunately, 1) an operational definition of "on" and "off" time was not provided in the protocol and 2) the CRF only recorded "off" time without differentiating between the 2 alternatives, "on" versus "on with dyskinesias." The latter may not necessarily represent a better state than "off" (no operational definition provided, but potentially fairly benign according to the patient diaries) and should not be represented as such.

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Recommendations:

An approvable letter can be issued. Proposed labeling should point out the limitations of the data, as collected. Specifically, 1) UPDRS III does not encompass the entire motor exam and 2) a decrease in "off" time is not simply an increase in "on" time.

/S/

John Feeney, M.D. /
Medical Reviewer
September 13, 1996

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Review and Evaluation of Clinical Data

Safety Review

Application Information

NDA 20-667

Pharmacia & Upjohn

NDA Submission Date: December 28, 1995

Drug Name

Generic: Pramipexole

Proposed Trade Name: Mirapex™

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 0.125 mg, 0.25 mg, 1.0 mg, 1.25 mg, and 1.5 mg

Proposed Use:

Pramipexole should be given T.I.D.. Dosages should be increased gradually from a starting dose of 0.375 mg/day and should not be increased any sooner than every 5-7 days. In most studies a 7 week dose escalation scheme was followed: 0.125 T.I.D., 0.25 T.I.D., 0.5 T.I.D., 0.75 T.I.D., 1.0 T.I.D., 1.25 T.I.D., and at the 7th week to the maximum dose of 1.5 T.I.D. Withdrawal should occur gradually over a 7-day period.

Safety Reviewers: John D. Balian, M.D. & James F. Knudsen, M.D., Ph.D.

Date of Review: November 13, 1996

1 Summary of Pramipexole Safety Review

Pharmacia & Upjohn is requesting approval to market pramipexole for the treatment of idiopathic Parkinson's disease (PD). Overall, the ISS summarized the safety experience for 1408 patients with about 815 person-years (PYs) of pramipexole use, most of it (800 PYs) coming from the PD trials. Both early therapy (ET) and advanced therapy (AT) PD patients had over 100 PYs of pramipexole exposure that occurred after the first year of use. In the completed PD studies, there were 245 ET and 176 AT patients who reached 4.5 mg/day, the maximum recommended daily dose. Of these 421 patients, 190 were exposed to this dose for at least 12 consecutive weeks.

In the clinical pharmacology studies, pramipexole had significant cardiovascular (CV) effects on healthy volunteers. Symptomatic orthostatic hypotension (OSH) was identified as a dose-related phenomenon, first evident following a single oral dose of 0.2 mg (first dose phenomenon). The OSH was reported as dose-limiting (0.4 mg/day was the maximum tolerated dose in study 26) for the normal volunteers. 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, but in those measured it was significant, with a decrease from baseline in SBP of up to 66 mg Hg and 30mmHg in DBP. The latter subject was unable to stand again for 8 hours and continued to experience nausea and asthenia for up to 12 hours. Overall, other symptoms associated with OSH were dizziness, asthenia, malaise, nausea, and increased sweating. There were no clinically significant changes from baseline in ECG parameters reported compared with placebo.

In the phase 2/3 studies, a separate review and analysis for the ET and AT patients was done (for this review) in order to adequately describe pramipexole associated AEs. In the 3 ET randomized controlled trials (RCT), the frequency of study dropout associated with non-serious AEs was comparable in the pramipexole and the placebo groups. The frequency of study dropout associated with serious AEs was 2% in pramipexole and 1% in the placebo patients, with only one pramipexole patient experiencing an AE that was CV in nature. The 3 most common AEs, irrespective of severity, associated with dropout in the 3 ET studies were: hallucinations, nausea and dizziness. Only 1 patient dropped out due to syncope. Overall, syncope as an AE was reported in 5 (1.3%) pramipexole-treated and 2 (1.0%) placebo treated patients. There were 4 deaths in pramipexole patients, 3 of which were CV in nature.

In the 4 AT RCTs, the frequency of study dropout associated with either serious or non-serious AEs was less in the pramipexole than in the placebo groups. None of the 18 patients exposed to pramipexole who had serious AEs had syncope, bradycardia, or orthostatic hypotension and only 3 patients had an event that could be considered CV in nature. There was no clear pattern of AEs associated with dropout. There were 8 deaths in pramipexole patients, 3 of which were CV in nature. Across the AT placebo controlled studies in the ISS,

only hallucinations and dry mouth were reported in more than 5% of pramipexole patients and were at least 2 times more frequent than in placebo. Syncope was reported in 2.2% of pramipexole AT patients compared to 3.4% of placebo patients.

Across all patients exposed to pramipexole in the development program, there were no AEs clinically consistent or suggestive of hepatic failure or necrosis, urolithiasis, agranulocytosis, or aplastic anemia. Rhabdomyolysis was reported in one patient. One patient developed acute thrombocytopenia. There were no significant shifts in ECG parameters and laboratory analytes from baseline to study endpoint.

In summary, pramipexole use was not associated with increased risk for deaths, serious AEs, or dropouts in PD patients. While there was a clear increase in CV effects (syncope and OSH) attributable to pramipexole in the phase 1 healthy volunteers, no significant differences from placebo were observed in the phase 2/3 trials.

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Table of Investigations
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Exposure by Maximum Dose
Emergent AEs in Phase 1-- 1% AE Table in Healthy Volunteers

Patients with Serious Aes

Emergent AEs-- 1% AE Table in ET Patients
Emergent AEs-- 1% AE Table in AT Patients
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Laboratory Values-- Predefined Normal Limits
Laboratory Values-- of Potential Concern
Summary of Patients with CPK Elevations
Summary of Patients with LFT Elevations

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2 Background

Boehringer Ingelheim (BI) in collaboration with the Pharmacia & Upjohn Company (Upjohn) developed pramipexole as a dopamine agonist for the "treatment of the signs and symptoms of idiopathic PD". Pramipexole is a synthetic amino-benzothiazole derivative with affinity for dopamine and α_2 receptors. It binds with highest affinity to the D₃ receptor subtype but it also binds the D₂ and D₄ receptors. It "stimulates fully" the dopamine receptors, with preclinical evidence of efficacy in animal models of Parkinson's disease (PD).

2.1 Overview of Safety Review

The sponsor had proposed for FDA approval to market pramipexole as primary therapy (referred in the NDA as monotherapy or early therapy {ET}) for Early Parkinson's Disease (EPD) and as adjunctive therapy (AT) for Advanced Parkinson's disease (APD), but at a pre-NDA meeting, the agency suggested that no specific referrals to monotherapy and adjunctive therapy be made, and instead a general claim for indication of "treatment of the signs and symptoms of idiopathic PD" be made.

In view of this, the sponsor's Integrated Safety Summary (ISS) provides pooled descriptions and analyses of the treatment emergent adverse events (AEs) without regard to ET or AT. The only separation of data in the ISS is that of data obtained from the so called "pivotal trials" or "the adequate and well controlled trials" and the rest of the data. These pivotal trials, consisting of 3 (studies M2730/0001, -/0004, and -/0010) double-blind, placebo-controlled, randomized controlled trials (RCTs) in PD, were designated as such for efficacy purposes, but the connotation and the analysis were then carried over by the sponsor to the safety analysis as well. The ISS contains 4 more similarly designed RCTs in PD, that were not designated as "pivotal" for efficacy purposes, and hence, for the safety review, the sponsor presents and analyzes these trials separately referring to them as "the other controlled PD trials".

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, we determined that it would be a better approach to separate the review and analysis of the ET and AT patient populations, wherever feasible. With the help of the sponsor a reanalysis of the data was performed. Since, there were no safety reasons to designate some studies as pivotal, data obtained from all similarly designed RCTs (3 studies from the ET trials and 4 from the AT trials) were used in the reanalysis.

This review, whenever possible reflects this separate (and not pooled) approach, except when specific findings from the "pivotal studies", after separating them into ET (trials 1 and 4) and AT (trial 10) are utilized.

2.2 Development of Pramipexole

According to the sponsor, development of pramipexole as a treatment for PD was pursued because preclinical studies suggested that it had effectiveness in reversing parkinsonian signs, no dopamine agonist is currently approved for monotherapy of PD, and pramipexole's "full dopamine agonism". Based upon this preclinical receptor profile, the sponsor hypothesized that pramipexole would have advantages in efficacy and/or safety when compared to approved dopamine agonists.

Pramipexole's clinical development program began in Europe with administration to healthy volunteers in January 1988. As of 1/1/96, pramipexole has not been marketed in other countries and there have been no foreign regulatory actions regarding its approval.

2.3 Pramipexole Preclinical Studies

Pramipexole binds to the D2 receptor subfamily, with highest affinity to the D₃ receptor subtype but it also binds the D₂ and D₄ receptors stimulating these receptors fully. In comparison, the ropinirole NDA review mentions bromocriptine and pergolide each with affinity for D1 and D2 receptor subtypes, and ropinirole and its metabolites with high affinity to the central D2 dopamine receptors, but not to D1.

In animal safety data, the no-toxic effect dose for pramipexole was reported to be 0.5 mg/kg/day for rats. The LD₅₀ of acute oral toxicity in mice was 1700 mg/Kg with signs of exophthalmos, piloerection, tremors, convulsions, and hypomotility. The LD₅₀ of acute IV toxicity in rats was 210 mg/Kg with signs of exophthalmos, dyspnea, convulsions, ataxia, and hypomotility. Autopsy in both cases revealed hemocongestion of major organs.

Chronic toxicology studies revealed mammary gland changes (proliferation of glandular epithelium) in female rats in the mid- (2 and 3 mg/kg/day) and high (8 and 15 mg/kg/day) dose groups. Other AEs noted were behavioral changes in both sexes, decreased body weight gain, and cholesterol and triglycerides in females in the lowest doses. With mid- and high-doses, body weight gain was reduced in both sexes. In addition, sporadic modest elevations in liver enzymes and decreases in potassium levels occurred. Hematologic AEs included mild thrombocytopenia. Organ changes included decrease in liver and thymus weights, and enlarged corpora lutea. Leydig cell hyperplasia was observed mainly in the low-dose groups and there were two adenomas observed in male rats (one control one pramipexole-treated).

Chronic toxicology studies in rhesus monkeys were significant for bradycardia and increased R-R and Q-T intervals observed in males of the mid-dose group.

The main findings observed in toxicology studies included retinal degeneration in

albino rats, CNS effects (increase in motor activity, agitation, ataxia, and tremors), and decreased prolactin secretion. Both male and female albino rats receiving long-term (2 year) pramipexole at mid- (2 mg/kg/day) and high (8 mg/kg/day) dose groups experienced dose-dependent retinal degeneration. The degeneration was characterized by loss of photoreceptor cells usually occurring late in treatment. Rats of the low dose group (0.3 mg/kg/day) and the control group were free of the AE. In other studies involving rats lasting only one year, and in long-term studies in other species (mice, swine, and monkeys) this syndrome was not recorded.

No reproductive abnormalities in mating, pregnancy, or pup development were noted in the low- and mid-dose groups of rats studied. In the high-dose, irregular estrus occurred in about one-half of the females, and the number of pregnancies that resulted in successful delivery decreased. Also the delivered pups had impaired growth during the lactation phase. The increase in the infertility and the impaired growth seen in the pups may be related to the drug's effect of inhibiting prolactin secretion. The teratogenicity data are scant due to the small number of pups, but no obvious effects were noted. Similar studies in rabbits were devoid of reproductive toxicities at doses up to 10 mg/Kg.

Mutagenicity studies were negative. Carcinogenicity studies in mice revealed no significant incidences of neoplastic lesions. Carcinogenicity studies in rats were significant for a higher incidence of Leydig cell adenomas in the mid- (2 mg/Kg/day) and (8 mg/Kg/day) high-dose groups. Leydig cell hyperplasia and testicular adenomas in rats were also observed in the ropinirole NDA review. Both sponsors attributed these to the reduced plasma prolactin that caused a reduction in Leydig cell LH receptors, which triggers a compensatory increase in LH production and release leading to Leydig cell hyperplasia and adenomas. (These Leydig cell LH receptors apparently are not present in humans).

Pramipexole rapidly crosses the blood-brain and blood-placental barriers in studied rats and is excreted in the milk of lactating mothers.

The opiate receptor activity of pramipexole was not investigated.

In summary, the main findings observed in the toxicology studies with pramipexole were related to retinal degeneration in albino rats, CNS effects, and reproductive effects possibly due to decreased prolactin secretion in rats (as the sponsor hypothesized).

2.4 Review of Safety Issues Identified in The Sponsor's Proposed Labeling

In the annotated labeling, pramipexole is described as a nonergot dopamine agonist with high specificity for the D2 subfamily receptors with a preferential affinity for D₃ receptors. The sponsor claims that by depressing dopamine synthesis, release, and

turnover, pramipexole reduces dopamine-induced neuronal degeneration in animals and alleviates parkinsonian motor defects.

In the current proposed label, pramipexole is indicated in "the treatment of the signs and symptoms of idiopathic Parkinson's disease", as was suggested by the agency at a pre-NDA meeting. In a communique dated October 31, 1996, the sponsor proposed a different text for the indications section to reflect our concentration of reviewing the AT and ET populations separately. The proposed text is: "Mirapex™ tablets are indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, both as first-line treatment (without levodopa) in early disease and in combination with levodopa for advanced Parkinson's disease".

The recommended starting dose is 0.375 mg/day in three divided doses, with a gradual increase every. . . days to a desired maintenance dose, with a maximum of 4.5 mg/day. Although abrupt discontinuations were uneventful, the sponsor recommends a gradual taper.

In the animal toxicology section, there is a mention of occurrence of Leydig cell adenomas in male rats, decreased fertility in female rats, and the excretion of drug-related material into breast milk.

Under the warnings section of the labeling, the sponsor mentions the occurrence of postural hypotension in patients treated with pramipexole and recommends gradual titration and careful adjustment of the dose. The sponsor claims that tolerance to the hypotension develops. Another AE mentioned under the warnings section is hallucinations: when used as monotherapy (EPD) 9% (34/377) of patients receiving pramipexole and 2% (5/222) of patients receiving placebo reported hallucinations. While in APD, this AE occurs more frequently, 21% (38/181) of patients receiving pramipexole in combination with carbidopa/levodopa vs 6% (10/178) of patients receiving placebo in combination with carbidopa/levodopa.

In the precautions section, the sponsor mentions that caution should be exercised when treating patients with renal insufficiency, and pramipexole may potentiate the dopaminergic side effects of levodopa and "may cause and/or exacerbate preexisting dyskinesia".

Under the AEs section of labeling, in pooled data for both ET and AT Parkinson's patients, 11% (out of 702) receiving pramipexole and 14% (out of 550) receiving placebo dropped out of the controlled studies due to AE occurrence. Hallucinations (3%), dizziness (2%), extrapyramidal syndrome (EPS) (1%), confusion (1%), somnolence (1%), postural hypotension (1%), and nausea (1%) were the most common reasons for withdrawal. These AE dropout risk estimates included all US and non-US experience and did not separate APD from EPD.

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 and AT studies (pooled). In table 1, events are listed if they occurred in more than 1% of the patients where the event rate was more than 2 fold greater than placebo.

Table 1. Adverse events that occurred in more than 1% of and were more than 2 fold greater in pramipexole ET patients than with placebo. (Taken from sponsor's proposed labeling which uses data from studies 1, 4, and 10.)		
	pramipexole	placebo
	N=558(%)	N=400(%)
Decreased Weight	1.6	0.2
Peripheral Edema	4.1	2.8
Twitching	1.6	0.8
Hallucination	12.7	3.8
Somnolence	18.3	8.0
Akathisia	1.2	0.2
Decreased Libido	1.1	0.2
Myoclonus	1.1	0.5
Paranoid Reaction	1.1	0.5
Vision Abnormality*	2.9	0.2
Diplopia	1.2	0.5

*Floaters, visual spots, and peripheral vision disturbance.

Increased risk of somnolence and hallucination was associated with pramipexole's use.

In the patient information section, the sponsor is recommending that patients avoid driving automobiles and using heavy machinery until they know how pramipexole will effect them.

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3 Methods of Safety Review

As mentioned in section 2.1, the sponsor has provided pooled data in the ISS (without regard to ET or AT), and presented the data in several formats: (1) adequate and well controlled PD trials (studies 1, 4, and 10--the studies designated as pivotal to the efficacy of pramipexole); (2) all completed PD trials; (3) ongoing PD trials; (4) all completed schizophrenia trials; and (5) pooled data. In the ISS, no distinctions are made between US and non-US trials (although no clear differences in design are apparent) or in ET vs AT trials. Again, as noted in section 2.1, this review follows a different format: separate data presentation for the ET and AT trials. The review focused on deaths, serious AEs, dropout risk, dropouts associated with AE occurrence, and common AEs.

Using both the paper and electronic (CANDA) versions of the NDA, treatment emergent AEs occurring with pramipexole use were evaluated separately in ET and AT patients. To verify the accuracy of the primary data that was available for review, the information listed in the data listings, the CRFs, and the death narratives were cross checked for accuracy. To evaluate the consistency and accuracy of the AE coding (WHOART in the BI studies and COSTART in the Upjohn studies), subsumed investigator verbatims were compared to the corresponding preferred WHOART and COSTART AE codes. To further examine the validity of AE coding, selected WHOART and COSTART 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 view of the high incidence rates of syncope in the non-ergot dopamine agonist ropinirole (currently under review as an antiparkinson's drug), any supporting data for patients coded with the WHOARTs and COSTARTs "blackout", "faintness", "syncope, postural", "syncope, vasovagal", "symptomatic orthostatic hypotension", "circulation failure" were reviewed focusing on evidence of syncope or general CV events. Investigator verbatims for CV COSTART codes in studies 1, 4, and 10 were also reviewed to evaluate their specificity.

Since deaths were observed in the RCTs, before patients entered extensions, pramipexole mortality was compared to that in placebo separately for ET and AT patients. For the rate comparison, the sponsor used the exact number of days in computing person-years (PYs). PYs were estimated based on the medication records: the exact number of days were computed for each patient.

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) all deaths; (2) serious AEs; (3) AEs associated with dropout; (4) AEs coded as syncope, bradycardia, ventricular tachycardia/fibrillation or peripheral edema; and (5) patients

with any AEs suggestive of agranulocytosis, aplastic anemia, thrombocytopenia, serious skin reactions such as Stevens-Johnson Syndrome, hepatic failure or necrosis, renal failure or worsening of renal function, rhabdomyolysis, urolithiasis, hematuria or urosepsis, and retroperitoneal fibrosis or pulmonary fibrosis.

The AE experience observed in individual trials was contrasted to confirm that no major discrepancies in reporting occurred. The US and non-US data was not contrasted, but there were no clear differences in design or reporting.

4 Review of Findings

4.1 Description of the Pramipexole Development Program

Pramipexole was developed as a collaborative research effort between Boehringer Ingelheim (BI) and The Pharmacia Upjohn (Upjohn) companies. Clinical development of pramipexole is being conducted under the following INDs:

was submitted by BI on _____ to initiate Phase II clinical trials. On the sponsorship of the IND was transferred to Upjohn.

Since other indications (schizophrenia and depression) are not sought at this time, most analysis and review refers to the PD trials, without ignoring the data obtained from all trials. No other NDA's have been previously submitted.

Appendix 4.1.1 provides a listing of all studies included in the ISS. The ISS described pramipexole treatment emergent AEs based upon observations from 19 Clinical Pharmacology studies, 16 completed phase II-III clinical trials, and 15 ongoing trials.

Of the 19 clinical pharmacology studies involving 297 (260 PPX and 37 placebo) subjects, 17 were conducted in healthy volunteers, 1 (protocol 60) was conducted in volunteers with impaired renal function, and 1 (n=3) was conducted in APD patients.

Of the 16 completed phase II-III clinical trials (i) 9 (studies---#1, 4, 17, and 21 in ET and studies---#10, 18, 19, 20, and 22 in AT) were PD studies involving 1253 (702 PPX and 551 placebo) patients; and (ii) 7 were completed studies in schizophrenia involving 322 (177 PPX, 50 comparator, and 95 placebo) patients. There are also 15 ongoing studies: (i) 10 ongoing PD studies involving both controlled and uncontrolled studies, the controlled studies are blinded so an exposure number is not available, while the uncontrolled ongoing studies involve 1056 patients of which only 529 are uniquely exposed, the other 527 were enrolled in the completed controlled studies and exposed to PPX; (ii) 3 ongoing studies in schizophrenia; and (iii) 2 ongoing studies in

depression.

A tabulation of patient accountability of the completed studies is detailed in table 4.1.1:

	Number of Patients			
	Pramipexole	Placebo	Comparator	Total
Phase I (Clinical Pharmacology)	260	37	-	297
Phase II/III (PD Total)	702	550	-	1252
EPD	416	262	-	678
APD	286	288	-	574
Phase II/III (Schizophrenia Studies)	177	95	50	322
Total Phase II/III	1139	645	50	1871

The sponsor has given the following numbering system to the trials: M2730/00x, where x stands for the number of the study, i.e. 1, 2, ..., 37, etc.. In this review, the final number (x) will be used to identify a study. The sponsor has selected three Phase II/III studies M/2730/0001 (study 1), M/2730/0004 (study 4), and M/2730/0010 (study 10) as the key studies for the evaluation of the effectiveness of pramipexole for the treatment of idiopathic PD (as discussed earlier, no specific referrals were made initially to either early or advanced PD in the indication). The sponsor chose these three trials since they met the criteria of adequate and well-controlled studies: studies with clear objectives, well defined methods of analysis, valid controls, and sufficient statistical power to allow a valid comparison with placebo.

As discussed earlier, the sponsor has presented safety data from all completed trials, but based the main safety analysis of this NDA submission on the 9 completed PD studies of phase II/III trials, and in particular the "pivotal" trials, pooling the data without regard to ET and AT populations. Again, as discussed earlier, the review did not follow this approach.

Of the 9 completed PD studies in phase II/III trials, 3 (studies 1, 17, and 18) were entirely conducted in the US, 2 (studies 4 and 10) were conducted in the US and Canada, and 4 (studies 19, 20, 21, and 22) were entirely foreign (non-US and non-Canadian) in conduct. All, except for study 20 were multicenter trials. Four trials (studies 1, 4, 21, and 17) were with patients not taking levodopa --defined as "early" PD-- while 5 (studies 10, 19, 20, 22, and 18) were with patients taking levodopa --defined as "advanced" PD. Of note, the three pivotal studies (1 and 4 with EPD and

10 with APD) were US and Canadian in conduct.

The three pivotal or as the sponsor refers to them "the adequate and well-controlled" studies were multicenter, randomized, double-blind, and placebo-controlled in patients with PD who were not taking levodopa (defined as "early")--(protocols 1 and 4), or in patients with PD who were maintained on optimal doses of levodopa (defined as "advanced")--(protocol 10). Protocols 1 and 10 were flexible-dose studies during which patients received treatment with placebo or pramipexole from mg/day with an initial ascending dose phase (up to 7 weeks), followed by a 24 week maintenance phase, and a 1 week dose-reduction phase. Protocol 4 was a dose-response, parallel study where patients received pramipexole 1.5, 3.0, 4.5, 6.0 mg/day, or matching placebo. There was a 6 week ascending dose phase, followed by a 4 week maintenance phase at the targeted dose, and 4-8 day dose-reduction period. All other completed PD studies were also double-blind and placebo-controlled with the exception of two pilot studies (17 and 18), which were single-blind. Otherwise, there were no significant differences in design between ET and AT studies or the US and the foreign studies.

Patients from PD studies 1, 4, 10, 17, 18, 19, 20, and 22 were given the option of enrollment in extension studies (the current ongoing studies). Table VIII.G-15 in the ISS (page 8/3/47) enumerates the patients participating in more than one PD study. The total number of patients enrolled in the ongoing PD studies is 1056, 527 enrolled from the pramipexole arm, 371 from the placebo arm of the completed PD RCTs, and the rest are new enrollees.

The only phase 2/3 studies with comparative designs were in schizophrenia trials.

4.2 Summary of Pramipexole's Pharmacokinetics

Pramipexole is rapidly absorbed with an approximate bioavailability of 90% (indicating minimal first pass metabolism) and peak plasma concentrations occurring approximately hours after dosing. Renal excretion (> 80%) is the primary route of elimination as unchanged parent compound and the elimination half-life is 8.5 hours in young volunteers and 12 hours in older volunteers. Clearance in healthy female volunteers was lower than in healthy male volunteers. Clearance is decreased significantly in renally impaired patients. Protein binding was less than 20%.

Since pramipexole has minimal first pass metabolism, no in vitro or in vivo studies were performed to determine the presence of a P450 pathway.

Increases in C_{max} and AUC were proportional with dose over the range mg. Food decreased the rate of pramipexole absorption at steady state both in PD patients and healthy volunteers.

The sponsor conducted a study to explore the potential influence of age on renal processing (drug elimination) in study 0069. Age did not influence the absorption of pramipexole, nor the apparent volume of distribution after oral administration, however, as expected, the mean clearance for the elderly patients was approximately 30% lower than the young volunteers. Also, as a result of the reduction in glomerular filtration with increasing age, there was an increase in the elimination half-life from approximately 8.5 hours to 12 hours. In patients with renal insufficiency pramipexole total clearance and renal clearance decreased by 70% and 91%, respectively. The potential influence of hepatic insufficiency on pramipexole pharmacokinetics was not evaluated.

4.3 Description of the ISS Population

As table 4.1.1 in section 4.1 shows, in the 9 phase 2/3 completed PD RCTs, there were 702 patients who were exposed to pramipexole. Of these, 416 and 286 were observed in ET and AT studies, respectively.

Appendix 4.3.1 shows the demographics of the RCTs. In these trials there were no statistically significant differences between the pramipexole and placebo groups with respect to age, sex or race. The demographic characteristics of the combined ET and AT population were generally representative of the expected demographics of PD patients. In the pramipexole exposed group, the ages ranged from , with an average of around 62.8 years and the vast majority of patients (61%) were between years old, while about 24% of the patients were >70 years of age. The overwhelming majority (96%) were Caucasian and 64% were male.

There was little difference in age between ET and AT patients across the ISS. AT patients had a longer duration of PD at baseline than that of ET patients; 9 years compared to years. The average UPDRS Part II and III (the efficacy variables analyzed) were lower in the ET groups. AT patients had received l-dopa therapy for about 7 years and were rated in Hoehn and Yahr Stage II-IV at baseline, while by definition (protocol inclusion criteria) ET patients could not have received l-dopa therapy and were rated as Hoehn and Yahr Stage I-III.

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 allowed continued use of amantadine, anticholinergic, and selegeline (l-deprenyl) therapy, but their dosage could not change. "Rescue" therapy with Sinemet was allowed, but exactly how this was applied was left up to each investigator.

Patients with clinically significant active cardiac disease were excluded from the trials. Disease co-morbidity prevalence was not compared in the ISS.

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

According to the sponsor, 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 including asymptomatic changes in laboratory findings, exacerbation of pre-existing conditions, intercurrent illnesses, and drug interactions.

Because of the dopamine agonist activity of pramipexole and because it caused hypotension and orthostatic hypotension in phase 1 studies, supine and standing BPs were collected across phase 2 and 3 studies. Patients were checked for postural changes by comparing 5 minute supine BPs with 1 minute standing BPs. In phase 2/3, while the method of BP measurement was standardized across studies, the timing of BP measurement with respect to drug dose was not standardized, unlike the phase 1 studies, where supine and standing BP were measured at specific time points following dosing. This sponsor uses postural hypotension and orthostatic hypotension interchangeably.

In coding the AEs, BI used the WHOART dictionary while Upjohn used the COSTART dictionary. As Upjohn took overall responsibility of the submission, it reassigned the WHOART preferred terms to COSTART preferred terms.

Because certain investigator verbatims were judged to be related to an event of particular interest, some specific coding rules were applied. The investigator verbatims "blackout spells", "fainting", "syncopal spells", "cardiovascular collapse", and "orthostatic collapse" were coded with the COSTART "syncope". The investigator verbatims "drowsiness", "sleepiness", and "sedation" were coded with the COSTART "somnolence".

There were instances of coding inconsistencies. For example, the adverse event descriptive term "fall" was subsumed under the COSTART terms gait abnormality, ataxia, and accidental injury. Other adverse events listed under more than one COSTART terms were "dizziness on standing", "faintness upon standing", and "lightheadedness". These were subsumed under COSTART terms postural hypotension of the cardiovascular body system, as well as under the COSTART term dizziness related to the CNS body system. The minor inconsistencies are not likely to influence the analysis, and overall, the sponsor's coding approach was found to be appropriate.

In reviewing the NDA, it appears that the approach described by the sponsor to ascertaining and describing treatment emergent AEs was followed in all studies. In addition to having the investigator code AEs as to degree of medical severity, the

sponsor identified AEs meeting the regulatory definition of serious. The ISS defines concurrent illness as any illness that occurred prior to study entry. These conditions were considered treatment emergent AEs if the conditions worsened during the course of the study.

The NDA summarized deaths, serious AEs, and overall dropouts from completed and ongoing studies using a cutoff date of 1/31/95. Patients had a unique identifier and most patients were counted only once except where placebo patients entered a pramipexole extension (371 patients). Two patients in the ISS were randomized to receive placebo but ended up not receiving any treatment.

In the ISS, the sponsor described common AE occurrence by focusing on AEs considered causally related to pramipexole. Potential causality was defined as a greater than 10% increase and greater than placebo. Since dose escalation was used in all clinical studies, a dose response analysis could have been confounded by time since first exposure. In addition, The sponsor 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 pramipexole by concurrent medications, underlying diseases, or in demographic subgroups, AEs that occurred $\geq 5\%$ were used to calculate relative risk (RR). Percentages of occurrence were calculated separately for ET and AT patients. The following concurrent medications were selected: selegiline, anticholinergic agents, amantadine, domperidone, beta blockers, thiazide diuretics, tricyclic antidepressants, acetylsalicylic acid, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and tocopherol. Concurrent illnesses defined as present at baseline, were coded to respective COSTART terms. The following concurrent diseases were selected: arthritis, CV disease, constipation, depression, dizziness, hypercholesterolemia, hypertension, insomnia, and prostate disease.

Appendix 4.15.1 shows the hematology, chemistry, and urinary laboratory analytes with predefined limits that were set as normal ranges. The sponsor identified patients with laboratory analytes at or above the value of potential clinical concern. For hepatic enzymes, clinical concern was set at 2.5 times the ULN. All study protocols required at least baseline and ending laboratory determinations with some studies requiring more frequent blood sampling. A complete listing of patients who dropped out associated with any laboratory analyte abnormality was provided.

All ET and AT studies had 12 lead electrocardiograms (ECGs) performed. All studies had a screening ECG, but the frequency of follow-up ECGs varied from only one

follow-up in study 4 to 6 follow-ups in study 10. All ECGs were available for review.

4.5 Audit Findings and Specificity of the AE Coding.

The investigator verbatims listed in the CRFs of the 17 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 COSTART coding of the investigator verbatims seemed reasonable except for the few instances mentioned in section 4.4. Of special note are the AEs of "dizziness on standing", "faintness upon standing", and "lightheadedness" which were listed under more than one COSTART term: postural hypotension or dizziness. Because of the coding inconsistencies (AEs listed under more than one COSTART term), the specificity of "orthostatic hypotension" may likely be reduced. The protocol definition of orthostatic hypotension for all studies in the ISS was defined as a decrease in systolic BP of 20 mm Hg and/or a decrease in diastolic of 10 mm Hg, irrespective of presence of symptoms.¹ However, in the ISS, the COSTART 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. 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 pramipexole 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.

Other COSTART codes were also applied in a non-specific way. Several reports of falls associated with use of pramipexole have been coded as "gait abnormality", "ataxia", or "accidental injury".

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 1, 4, and 10 were also reviewed and nothing unusual in the reporting system was found. This review focused on obvious inconsistencies and biases and didn't use formal sampling to statistically test for potential bias.

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¹ We will use this definition to reflect objective orthostatic hypotension in subsequent discussion.