

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020667

STATISTICAL REVIEW(S)

DECISION
OCT 25 1996

Statistical Review and Evaluation

NDA: 20-667

Applicant: The Upjohn Company

OCT 24 1996

Name of Drug: Pramipexole Tablets

Documents Reviewed: Vols. 324-325, 344, 346, 355

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Background

The sponsor has submitted a total of five (5) controlled trials in support of Pramipexole (PX) for the treatment of Parkinson's disease. This review is restricted to the 3 large trials designated 'adequate and well-controlled' by the sponsor. The sponsor has designated the other 2 as 'supportive'. Trials 0001 and 0004 enrolled patients with early asymptomatic, idiopathic Parkinson's disease who were not receiving replacement levodopa therapy. Trial 0010 used PX as an adjunct to levodopa replacement therapy in patients with less than optimal response to levodopa as characterized by the presence of motor fluctuations.

Trial 0001 used stratified randomization (current selegiline use or not) among 26 centers in the US. Three hundred thirty-five (335) patients were randomized to either placebo or the PX group which experienced a 7 week dose escalation period (7 doses up to 4.5 mg/day) followed by a 24 week maintenance period.

The primary efficacy endpoint was the sum of scores of Parts II (13 activities each rated in increasing severity from 0-4) and III (14 components of physical status each rated in increasing severity from 0-4) of the UPDRS (Unified Parkinson's Disease Rating Scale). Secondary endpoints included 1) Time to Failure (worsening of disease or unsatisfactory therapeutic effect - time until patient requires levodopa), 2) Modified Hoehn and Yahr Scale, and 3) individual components (Parts II and III) of the UPDRS. The sample size of 150/arm was derived using Part III of the UPDRS results from DATATOP. The result follows from designing 90% power to find a treatment arm difference of change from baseline between 1.8 and 3.6 using a standard deviation of 5.0.

The primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The subset of those who actually entered the maintenance period was added before the data was unblinded and was intended to confirm the robustness of the results using primary data set. The primary analytic technique stated in the protocol was two-way ANOVA with interaction of treatment and center always in the model.

Trial 0004 randomized 264 patients among 20 centers in the US and Canada. Patients were randomized to either placebo or one of 4 doses of PX: 1.5, 3.0, 4.5 or 6.0 mg/day. The dose escalation phase lasted 6 weeks followed by a 4 week maintenance period.

The primary efficacy endpoint was the sum of scores of Parts I-III of the UPDRS. The secondary endpoints were the individual components of the UPDRS and the Hoehn and Yahr scale. The sample size of 50/arm was derived using the sum of parts II and II from a previous study. From a dose-response point of view, there was 80% power to detect a slope of 1.25 or, from a change from baseline point of view, there was 82% power to detect a difference of 5.8 between the 4.5 mg/day and placebo groups.

As in **Trial 0001**, the primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The subset of those who actually entered the maintenance period was added before the data was unblinded. With regard to the primary analytic technique, the protocol states only: "In this dose-response study, the primary variables will be analyzed by regression methods."

Trial 0010 (not conducted under an IND) randomized 360 patients among 26 centers in the US (22) and Canada (4). Patients were randomized to either placebo or the PX group which experienced a 7 week dose escalation period (from mg/day) followed by a 24 week maintenance period. Patients who dropped from the trial prior to completing at least one-half of the visits during the maintenance dose interval during the double-blind part of the trial were to be replaced unless the patient was dropped from the trial because of intolerable adverse events which included worsening of the underlying Parkinson's disease.

The primary efficacy endpoints were the following: 1) Part II of the UPDRS for both 'on' and 'off' periods and 2) Part II for 'on' periods, only. Secondary endpoints included 1) Part II 'on' and 'off' separately), 2) Modified Hoehn and Yahr Scale for 'on' and 'off' periods and a myriad of other analyses. As with **Trial 0001**, the protocol-specified sample size of 150/arm was derived using Part III of the UPDRS results from DATATOP.

The primary data set for analysis was to be all patients who had at least one dose and who had at least one post-baseline measurement. The primary analytic technique was two-way ANOVA with interaction of treatment and center always in the model. AUC was also conducted as a longitudinal analysis. The timed walking test (50 feet) was analyzed using change from baseline.

Note: All figures and graphs were produced by the sponsor.

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Results

In general, all reported results are for the LOCF analysis at the last visit during the maintenance period. This review reports only the intent-to-treat (ITT) results since similar results are obtained using only patients who entered the maintenance period.

There was no evidence of treatment by center interaction in any trial.

Trial 0001

Two (2) patients did not have any post-baseline measurements. Thus the ITT data set consists of 333 patients.

Table 1 displays the baseline characteristics of all randomized patients. There were no important treatment imbalances.

Table 2 displays the numbers of patients completing each phase of the trial. Approximately 80% of the patients completed the maintenance period.

Tables 3, 4, and 5 display the changes from baseline and statistical results for Parts II, III, and by selegiline and anti-cholinergic status, respectively. Patients treated with PX clearly improved their symptoms relative to those on placebo. On average, the LOCF change from baseline of patients who discontinued from the PX arm (N=16) was better than that of dropouts from the placebo arm (N=24): -.94 on PX, 1.58 on PBO for Part II, and -.63 on PX, 5.04 on PBO for Part III.

Tables 6 and 7 display the changes from baseline for the separate components of Parts II and III, respectively.

The distribution of Hoehn and Yahr scale scores also reflected a treatment effect: improvement from baseline: 27% PX, 16.5% PBO, worsening from baseline: 16.7% PX, 23.5% PBO.

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The time to treatment failure analysis using the logrank test ($p=.0015$) also indicates a treatment benefit: 5 patients failed in the PX group while 22 failed in the PBO group.

There was no indication of differential treatment effect by age, race or gender.

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Trial 0004

Table 8 displays the treatment group baseline characteristics and Table 9 displays the numbers of patients completing each phase of the trial. Approximately 90% of the patients completed the maintenance phase.

Table 10 displays the statistical results for the primary endpoint using the assigned dose as the treatment group: sum of all 3 parts of the UPDRS. Each dose was statistically different from placebo using even a conservative multiple comparison rule such as a simple Bonferroni adjustment. The sponsor states that "there was no dose-response relationship for efficacy apparent across the range of pramipexole doses studied".

With placebo in the analysis, a linear dose-response trend was detected with a p-value of .03 using the assigned dose group and .005 using the dose actually received.

When Parts II and III were analyzed separately, the overall test was statistically significant in favor of PX for part III but not for part II. See Tables 11 and 12.

Table 13 displays the results for the individual components of Parts II and III which showed the greatest average change from baseline.

Table 14 displays the distribution of patients who improved or worsened from baseline on the Hoehn and Yahr Scale. Approximately twice the number of patients on the 3 highest doses of PX improved from baseline compared to the number who improved on placebo.

Comment

The obvious question about this trial is why there was no statistical difference between drug and placebo for Part II of the UPDRS unlike the result in Trial 0001. The standard deviations are the same in both trials (3.0). Comparing Table 3 to Table 11 indicates that the average treatment difference was approximately 2.3 units in Trial 0001 as opposed to 1.5 in Trial 0004. The average change from baseline on drug was 0.5 units less in the latter trial. The slightly smaller overall sample size in Trial 0004 contributed to some extent.

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Trial 0010

Table 15 displays the baseline information for the treatment groups.

Table 16 displays the number of patients who completed each stage of the study. Approximately 80% of the patients completed the trial, a completer being one who "completed at least half of the visits during the maintenance-dose interval (i.e., through Visit 15) or any patient who discontinued trial medication because of intolerable adverse events".

Figure 1 and Table 17 display the results when averaging the 'on' and 'off' periods for Part II of the UPDRS using LOCF.

Figure 2 and Table 18 display the results of Part III of the UPDRS using LOCF. The sponsor did not report the results for just the 'on' period as it stated it would in the report. However, the protocol makes no mention of restricting Part III to the 'on' period.

Figures 3 and 4 display the results over time for the two respective primary endpoints. The profiles are very similar to those using LOCF, indicating that there is little effect of dropouts on the LOCF analyses.

In summary, the LOCF analyses were statistically significant on both primary endpoints.

Secondary endpoints which reached nominal significance were Part II 'off' periods ($p < .001$), Part II 'on' periods ($p = .004$), average percentage 'off' time calculated from patient diaries ($p < .001$, see Table 19 and Figure 5), levodopa dosage ($p < .001$), Schwab-England Disability Scale ($p < .001$) for 'off' periods and $P = .01$ for 'on' periods, and Modified Hoehn and Yahr Scale ($p < .001$). The timed walking test was not statistically significant.

Subgroup analyses

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The sponsor investigated demographic subgroups and the possibility of an interaction between selegiline (l-deprenyl) and pramipexole. The demographic analyses did not produce any evidence of interactions between treatment difference and age, race or gender. In Trials 0001, 0004 and 0010, 67%, 61% and 54% of the patients were taking selegiline, respectively. Table 20 (Trial 0004) displays the mean changes from baseline for active drug groups and placebo for patients who were and were not taking selegiline on study. Table 21 (Trial 0010) displays results for only patients taking selegiline and for the full data set. In Trial 0004, the differences from placebo were larger among patients who did not take selegiline at the two highest doses of pramipexole. This may be partially explained by the larger placebo effect among the selegiline-taking patients. None of the trials provide substantial evidence of an interaction between pramipexole and selegiline use.

Conclusion

Trials 0001 and 0004 provide statistically significant evidence of efficacy in patients with early PD. Trial 0001 was dose ranging up to 4.5mg/day. In trial 0004, although 6.0mg/day was slightly numerically superior to 1.5mg/day on the total UPDRS, there was no statistical evidence that it is in fact more effective than 1.5mg/day.

Trial 0010 provides statistical evidence of efficacy of a dose-ranging regimen of PX of up to 4.5mg/day as an adjunct to l-dopa therapy in patients with motor fluctuations.

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TABLE 1

Demographic Characteristics of Patients at Screen

Patient Data	Number (%) of Patients		
	Pramipexole (N=164)	Placebo (N=171)	P-Value
Age (yrs)			
<65	76 (46.3)	87 (50.9)	0.183
≥65	88 (53.7)	84 (49.1)	
Mean	63.4	62	
S.E.	0.78	0.88	
Min	33	30	
Max	85	85	
Sex			
Male	105 (64.0)	98 (57.3)	0.185
Female	59 (36.0)	73 (42.7)	
Race			
White	156 (95.1)	161 (94.1)	0.740
Black	2 (1.2)	4 (2.3)	
Other	6 (3.7)	6 (3.5)	
Weight (lbs)			
Mean	168.6	168.2 (N=169)	0.856
S.E.	2.48	2.79	
Min	101	96	
Max	260	282	
Height (in)			
Mean	67.1	66.9 (N=170)	0.631
S.E.	0.3	0.33	
Min	58	54	
Max	75	76	
Smoking History			
Nonsmoker	79 (48.2)	98 (57.3)	0.010
Ex-smoker	76 (46.3)	56 (32.8)	
Smoker	9 (5.5)	17 (9.9)	
Use of Alcohol			
Never Drinks	55 (33.5)	66 (38.6)	0.689
Average Consumption	108 (65.9)	104 (60.8)	
Excessive Consumption	1 (0.61)	1 (0.58)	
Duration of Parkinson's Disease			
Mean	2	1.7	0.097
S.E.	0.16	0.12	
Min	0	0	
Max	11.6	7.2	
UPDRS Part II (ADL) Total Score			
Mean	8.2 (N=163)	8.2	0.982
S.E.	0.31	0.33	
Min	1	1	
Max	20	22	
UPDRS Part III (Motor Examination) Total Score			
Mean	18.8 (N=162)	18.7 (N=170)	0.958
S.E.	0.71	0.71	
Min	1	3	
Max	63	53	
Modified Hoehn & Yahr Scale			
Mean	1.9 (N=163)	1.9	0.643
S.E.	0.04	0.05	
Min	1	1	
Max	3	3	
Current L-deprenyl Use			
Yes	112	113	0.480
No	52	58	
Current Anti-cholinergic Use			
Yes	19	24	0.511
No	145	147	

Source: Appendix C: Table 3.

Abbreviations: ADL = Activities of Daily Living.

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TABLE 2

Disposition of Patients Enrolled in the Study

Disposition	Treatment Group	
	PPX	PBO
No. of Patients Randomized	N=164	N=171
No. (%) of ITT ^a Patients	163 (99)	170 (99)
No.(%) of Patients Completing Ascending-dose Phase	152 (93)	161 (94)
No.(%) of Patients Completing Maintenance Phase	136 (83)	137 (80)
No.(%) of Patients Discontinuing Study	28 (17)	34 (20)
Reason for Discontinuation		
Adverse Events		
Worsening of Disease ^b	4 (2)	15 (9)
Worsening of Other Pre-existing Disease	0 (0)	1 (1)
Other	18 (11)	8 (5)
Unsatisfactory Therapeutic Effect ^c	1 (1)	7 (4)
Protocol Violation	1 (1)	0 (0)
Lost to Follow-up	2 (1)	0 (0)
Withdrawal of Consent	2 (1)	2 (1)
Other	0 (0)	1 (1)

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Source: Appendix C: Table 2.1.

^a Intent-to-treat, the number of patients in each treatment group is the number randomized who received at least one dose of study drug and with at least one post-baseline follow-up.

^b Defined as worsening of Parkinson's disease.

^c Defined as no deterioration but still unsatisfactory therapeutic effect.

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TABLE 3

Adjusted^a Mean Change from Baseline in UPDRS Part II Total Score^b,
Maintenance Interval
Intent-to-Treat - All Patients, LOCF

Treatment Group	Baseline ^c	Maintenance Week					
		0 ^d	4	8	12	16	24
PPX (N=163)	8.2	-2.5	-2.5	-2.4	-2.3	-2.4	-1.9
PBO (N=170)	8.3	-0.9	-0.7	-0.4	-0.2	0	0.4
P-Value	-	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 9.2.

^a Adjusted by investigator and investigator-by-treatment interaction.

^b Sum of 13 components of UPDRS Part II.

^c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^d Week 0 is the endpoint of the ascending-dose interval.

TABLE 4

Adjusted^a Mean Change from Baseline in UPDRS Part III Total Score^b,
Maintenance Interval
Intent-to-Treat - All Patients, LOCF

Treatment Group	Baseline ^c	Maintenance Week					
		0 ^d	4	8	12	16	24
PPX (N=162)	18.8	-6	-5.4	-5.2	-5.2	-5.1	-5
PBO (N=168)	18.8	-2.6	-2.3	-1.6	-0.9	0.4	0.8
P-Value	-	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001	≤0.0001

Source: Appendix C: Table 10.2.

^a Adjusted by investigator and investigator-by-treatment interaction.

^b Sum of 14 components of UPDRS Part III.

^c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.

^d Week 0 is the endpoint of the ascending-dose interval.

TABLE 5

Mean Change From Baseline in UPDRS
Parts II and III, Total Score by L-deprenyl and Anti-cholinergic Usage;
All Patients

Concomitant Therapy	Treatment Group	Part II ^a				Part III ^b			
		N	Yes	N	No	N	Yes	N	No
l-deprenyl	PPX	112	-1.9	51	-1.5	111	-4.6	51	-4.6
	PBO	112	0.3	58	0.7	112	1.3	57	1.5
Anticholinergic	PPX	19	-1.3	144	-1.9	19	-4.5	143	-4.6
	PBO	24	0.1	146	0.4	24	1.4	145	1.4

Source: Appendix C: Tables 11.1A & 12.1A.

^a Sum of 13 components of UPDRS Part II.

^b Sum of 14 components of UPDRS Part III.

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TABLE-6
 UPDRS Part II Individual Components
 Mean Change From Baseline to Endpoint
 All Patients

UPDRS Component	Treatment Group	
	PPX N=163	PBO N=170
Speech	0.0	0.0
Salivation	0.0	-0.1
Swallowing	0.0	0.0
Handwriting	-0.3	0.0
Cut food/handling utensils	-0.2	0.0
Dressing	-0.2	0.1
Hygiene	-0.1	0.0
Turning in bed/adjusting clothes	-0.3	0.1
Falling	0.0	0.0
Freezing when walking	0.0	0.1
Walking	-0.1	0.0
Tremor	-0.4	0.0
Sensory complaints related to Parkinsonism	-0.1	0.1

TABLE 7

UPDRS Part III Individual Components
 Mean Change From Baseline to Endpoint
 All Patients

UPDRS Component	Treatment Group	
	PPX N=163	PBO N=170
Speech	-0.1	0.1
Facial expression	-0.1	0.0
Tremor at rest (face)	-0.1	0.0
Tremor at rest (Left Hand)	-0.2	0.0
Tremor at rest (Right Hand)	-0.3	0.0
Tremor at rest (Left Foot)	-0.1	0.0
Tremor at rest (Right Foot)	-0.1	0.0
Action or postural tremor of hands (Left Hand)	0.0	0.0
Action of postural tremor of hands (Right Hand)	-0.1	0.0
Rigidity (neck)	-0.1	0.0
Rigidity (left upper extremity)	-0.3	0.0
Rigidity (right upper extremity)	-0.3	0.0
Rigidity (left lower extremity)	-0.1	0.1
Rigidity (right lower extremity)	-0.1	0.0
Finger taps (left)	-0.4	0.1
Finger taps (right)	-0.4	0.1
Hand movements (left)	-0.4	0.1
Hand movements (right)	-0.3	0.1
Rapid alternating movements (Left Hand)	-0.2	0.1
Rapid alternating movements (Right Hand)	-0.3	0.1
Leg agility (left)	-0.1	0.1
Leg agility (right)	-0.2	0.1
Arising from chair	0.0	0.2
Posture	0.0	0.1
Gait	-0.1	0.0
Postural stability	-0.1	-0.1

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TABLE 8

SELECTED DEMOGRAPHIC AND BASELINE FACTORS

Parameter	Pramipexole - assigned dose				Placebo n=51	P value
	1.5 mg/day n=54	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55		
age (mean years)	60.2	62.2	62.7	62.8	60.4	0.67
sex (% male)	64.8	62.0	63.0	69.1	62.8	0.90
race (% caucasian)	96.3	98.0	96.3	98.2	96.1	0.58
duration of disease (mean years)	1.8	2.0	1.9	2.3	1.6	0.16
current selegiline use (% yes)	55.6	66.0	66.7	58.2	58.8	0.65
UPDRS total score (mean points)	29.0	28.3	27.3	32.9	28.7	0.08
Hoehn and Yahr score (mean points)	1.8	1.9	1.8	1.9	1.8	0.52

TABLE 9

PATIENT DISPOSITION AND TOLERABILITY - NUMBER PATIENTS (%)

Endpoint	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
Number randomized	54	50	54	55	51
number (%) completing ascending dose	47 (87.0)	48 (96.0)	52 (96.3)	47 (85.5)	51 (100.0)
number (%) completing maintenance	44 (81.5)	48 (96.0)	50 (92.6)	46 (83.6)	50 (98.0)
number (%) completing at assigned dose - tolerability	44 (81.5)	46 (92.0)	43 (79.6)	37 (67.3)	49 (96.1)
number (%) completing with one or no dose reductions	44 (81.5)	48 (96.0)	50 (92.6)	44 (80.0)	50 (98.0)
number (%) dose limited during ascending dose interval due to clinical intolerance	2 (3.7)	3 (6.0)	7 (13.0)	10 (18.2)	1 (2.0)

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TABLE 10

UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	28.5	28.3	27.3	32.9	28.7
mean change*	-6.1	-5.8	-6.6	-7.1	-1.2
pairwise p value vs placebo	0.0027	0.0057	0.0008	0.0003	--
overall p value	0.0022	--	--	--	--

*Adjusted for center effect and treatment by center interaction

TABLE 11

UPDRS PART II - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	8.0	8.0	7.3	8.8	8.2
mean change*	-1.8	-1.9	-1.8	-1.8	-0.3
pairwise p value vs placebo**	N.D.	N.D.	N.D.	N.D.	N.D.
overall p value	0.0613	--	--	--	--

*Adjusted for center and treatment by center interaction

**N.D. - not done since overall p value not significant

TABLE 12

UPDRS PART III - CHANGE FROM BASELINE

Parameter	Pramipexole - Assigned Dose				Placebo n=51
	1.5 mg/day n=53	3.0 mg/day n=50	4.5 mg/day n=54	6.0 mg/day n=55	
baseline	19.4	19.3	19.2	22.9	19.6
mean change*	-4.2	-3.8	-4.7	-5.1	-0.6
pairwise p value vs placebo	0.0052	0.0151	0.0016	0.0005	--
overall p value	0.0048	--	--	--	--

*Adjusted for center and treatment by center interaction

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TABLE 13

**UPDRS PART II - INDIVIDUAL ITEMS WITH
GREATEST MEAN CHANGE FROM BASELINE**

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
handwriting	-0.4	-0.4	-0.4	-0.4	0.0
dressing	-0.1	-0.3	-0.3	-0.3	-0.1
tremor	-0.1	-0.3	-0.2	-0.3	-0.1

**UPDRS PART III - INDIVIDUAL ITEMS WITH
GREATEST MEAN CHANGE FROM BASELINE**

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
tremor - left hand	-0.2	-0.3	-0.2	-0.4	0.0
tremor - right hand	-0.1	-0.2	-0.3	-0.4	0.0
tremor - left foot	0.0	-0.1	-0.3	0.0	0.0
rigidity - neck	-0.1	0.0	-0.2	-0.3	0.1
rigidity - left upper extremity	-0.2	-0.2	-0.4	-0.2	-0.1
rigidity - right upper extremity	-0.2	-0.3	-0.3	-0.3	-0.1
rigidity - right lower extremity	0.0	-0.3	-0.2	-0.1	0.0
finger taps - left	-0.4	-0.2	-0.3	-0.3	-0.1
finger taps - right	-0.6	-0.2	-0.2	-0.3	0.0
hand movements - left	-0.2	-0.2	-0.3	-0.2	0.1
hand movements - right	-0.3	-0.1	-0.3	-0.3	0.0
rapid alternating movements - left	-0.2	-0.3	-0.2	-0.1	0.2
rapid alternating movements - right	-0.4	-0.2	-0.2	-0.2	0.1
bradykinesia	-0.3	-0.2	-0.2	-0.3	0.0

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TABLE 14

MODIFIED HOEHN AND YAHR SCALE - PERCENT CHANGE

Category	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
improved from baseline (%)	19.2	36.7	25.0	30.2	13.7
worsened from baseline (%)	17.3	6.1	5.8	9.4	25.5

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TABLE 15

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Characteristics	Placebo N=179	Pramipexole N=181	Total N=360
Age (yrs)			
N	179 (100%)	181 (100%)	360 (100%)
< 65	90 (50.3%)	85 (47.0%)	175 (48.6%)
>65	89 (49.7%)	96 (53.0%)	185 (51.4%)
Mean	179	181	360
S.E.	63.3	63.4	63.3
Range	0-72	0-72	0-81
Sex			
Male	116 (64.8%)	119 (65.7%)	235 (65.3%)
Female	63 (35.2%)	62 (34.3%)	125 (34.7%)
Race			
White	172 (96.1%)	172 (95.0%)	344 (95.6%)
Black	4 (2.2%)	3 (1.7%)	7 (1.9%)
Other	3 (1.7%)	6 (3.3%)	9 (2.5%)
Height (cm)			
N	179	178	357
Mean	170.3	170.6	170.6
S.E.	0.75	0.77	0.74
Range			
Weight (kg)			
N	179	180	359
Mean	72.9	73.7	73.3
S.E.	1.23	1.06	0.91
Range			
Duration of Parkinson's Disease (yrs)			
N	179	181	360
Mean	5.0	5.4	5.2
S.E.	0.39	0.45	0.36
Range			
Smoking History			
Non-smoker	95 (53.1%)	103 (56.9%)	198 (55.0%)
Ex-smoker	63 (35.2%)	70 (38.7%)	133 (36.9%)
Smoker	15 (8.4%)	8 (4.4%)	23 (6.4%)
Use of Alcohol			
Never Drinks	62 (46.4%)	76 (42.0%)	138 (44.2%)
Average Consumption	96 (53.6%)	105 (58.0%)	201 (55.8%)
Current L-dopamine Use			
No	85 (47.5%)	80 (44.2%)	165 (45.8%)
Yes	94 (52.5%)	101 (55.8%)	195 (54.2%)
Current Anticholinergic Use			
No	158 (88.3%)	155 (85.6%)	313 (86.9%)
Yes	21 (11.7%)	26 (14.4%)	47 (13.1%)
UPDRS Part II: 'on' Total Scores			
N	179	181	360
Mean	7.7	7.8	7.8
S.E.	0.40	0.40	0.28
Range			
UPDRS Part II: 'off' Total Scores			
N	177	181	358
Mean	17.4	17.4	17.4
S.E.	0.48	0.52	0.36
Range			
UPDRS Part III Total Scores			
N	179	181	360
Mean	23.3	22.8	23.0
S.E.	0.94	0.97	0.67
Range			
Modified Hoehn and Yahr Scale 'on'			
0	1 (0.6%)	1 (0.6%)	2 (0.6%)
1	3 (1.7%)	3 (1.7%)	6 (1.7%)
1.5	6 (3.4%)	3 (1.7%)	9 (2.5%)
2	55 (30.7%)	57 (31.5%)	112 (31.1%)
2.5	37 (20.7%)	25 (13.8%)	62 (17.2%)
3	34 (19.0%)	38 (21.0%)	72 (20.1%)
4	2 (1.1%)	5 (2.8%)	7 (1.9%)
N	179	181	360
Mean	2.3	2.3	2.3
S.E.	0.04	0.04	0.03
Range			
Modified Hoehn and Yahr Scale 'off'			
1	3 (1.7%)	1 (0.6%)	4 (1.1%)
1.5	36 (20.2%)	27 (14.9%)	63 (17.5%)
2	37 (20.7%)	53 (29.3%)	90 (25.1%)
2.5	68 (38.0%)	62 (34.3%)	130 (36.2%)
3	23 (12.8%)	29 (16.0%)	52 (14.5%)
4	11 (6.2%)	9 (5.0%)	20 (5.6%)
N	179	181	360
Mean	2.9	3.0	2.9
S.E.	0.06	0.06	0.04
Range			
Chest X-ray Findings			
Normal	125 (70.2%)	114 (64.0%)	239 (67.1%)
Abnormal	53 (29.8%)	64 (36.0%)	117 (32.9%)

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TABLE 16

Disposition for Patients Randomized Into the Trial

	Number of Patients (%)		
	PRAMIPEXOLE	PLACEBO	TOTAL
Number of Patients Randomized	181 (100)	179 ¹ (100)	360 (100)
Number of Patients Treated	181 (100)	178 ¹ (99.4)	359 (99.7)
Number of Patients Who Completed the Trial	151 (83.4)	140 (78.2)	291 (80.8)
Number of Patients Who Prematurely Discontinued	30 (16.6)	39 (21.8)	69 (19.2)
Discontinued Due To:			
Adverse Events			
Worsening of Disease Under Trial	3 (1.7)	9 (5.0)	12 (3.3)
Worsening of Pre-Existing Diseases	0 (0.0)	3 (1.7)	3 (0.8)
Other Adverse Events	21 (11.6)	18 (10.1)	39 (10.8)
Lack of Efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Administrative Reasons			
Protocol Violation	1 (0.6)	0 (0.0)	1 (0.3)
Lost to Follow-up	0 (0.0)	2 (1.1)	2 (0.6)
Withdrawal of Consent	4 (2.2)	3 (1.7)	7 (1.9)
Other	1 (0.6)	4 (2.2)	5 (1.4)

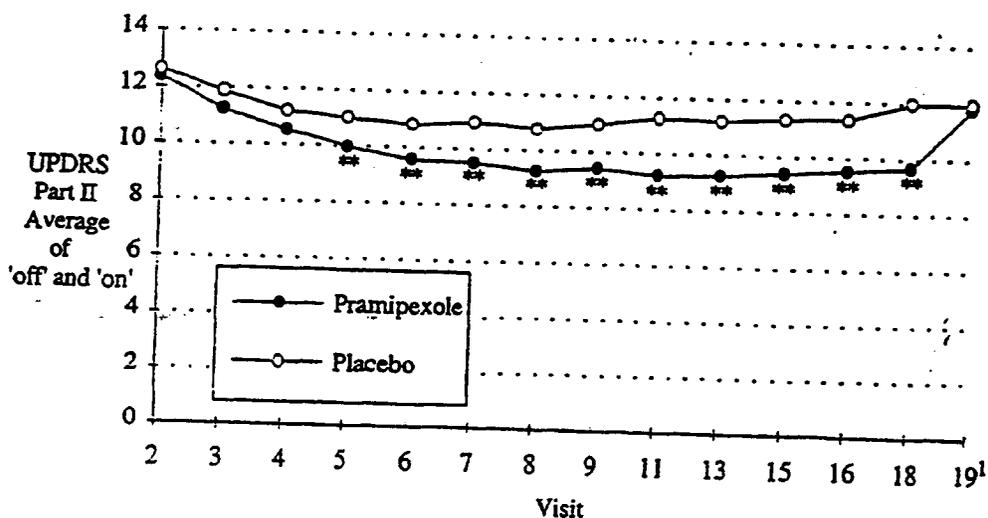
Source Data: Appendices 15.12 LISTING 1.1, 15.12 LISTING 7.1, 15.12 LISTING 7.2

¹ One patient (1054, Center 7) was randomized into the placebo treatment group but discontinued prior to receiving drug.

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FIGURE 1



Average UPDRS Part II 'off and 'on' Means by Visit.
Last Observation Carried Forward Analysis

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TABLE 17

Adjusted¹ UPDRS Part II Average of 'off and 'on' Period Means, Sample Sizes, and p-values for Change from Baseline and Area Under the Curve.

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (11-18)	OC Area Under the Curve over Maintenance Visits (11-18)
Pramipexole	-2.72 n = 179	-2.83 n = 171	-56.86 n = 179	-54.29 n = 134
Placebo	-0.47 n = 171	-0.46 n = 156	-17.63 n = 171	-17.36 n = 124
p-value	≤ 0.0001	≤ 0.0001	≤ 0.0001	≤ 0.0001

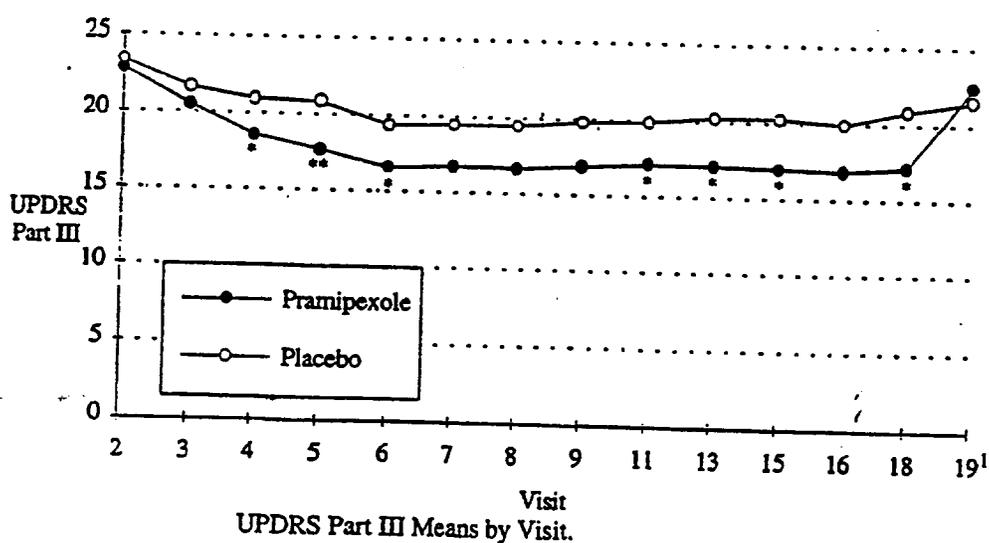
Source Data: Appendix 15.9.2 STATDOC 4.1.3.1, 4.1.3.2, 4.1.5.1 & 4.1.5.2

¹ Adjusted by center and center-by-treatment interaction (as per protocol).

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FIGURE 2



UPDRS Part III Means by Visit.

Last Observation Carried Forward Analysis

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TABLE 18

Adjusted¹ UPDRS Part III Means, Sample Sizes, and p-values for Change from Baseline and Area Under the Curve.

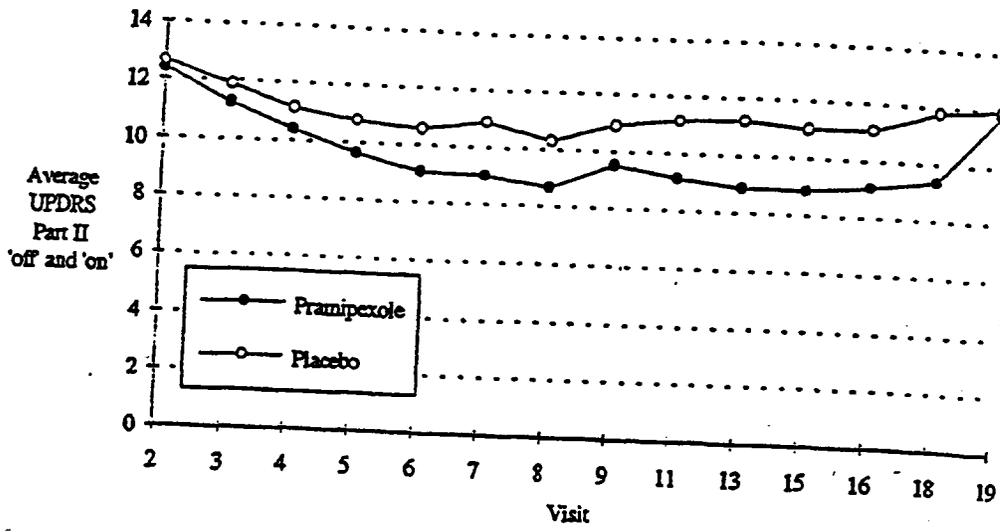
	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (11-18)	OC Area Under the Curve over Maintenance Visits (11-18)
Pramipexole	-5.64 n = 179	-5.73 n = 170	-113.84 n = 179	-125.60 n = 148
Placebo	-2.79 n = 171	-3.65 n = 157	-63.53 n = 171	-74.78 n = 133
p-value	0.01	0.08	0.01	0.02

Source Data: Appendix 15.9.2 STATDOC 4.2.3.1, 4.2.3.2, 4.2.5.1 & 4.2.5.2

¹ Adjusted by center and center-by-treatment interaction (as per protocol).

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FIGURE 3

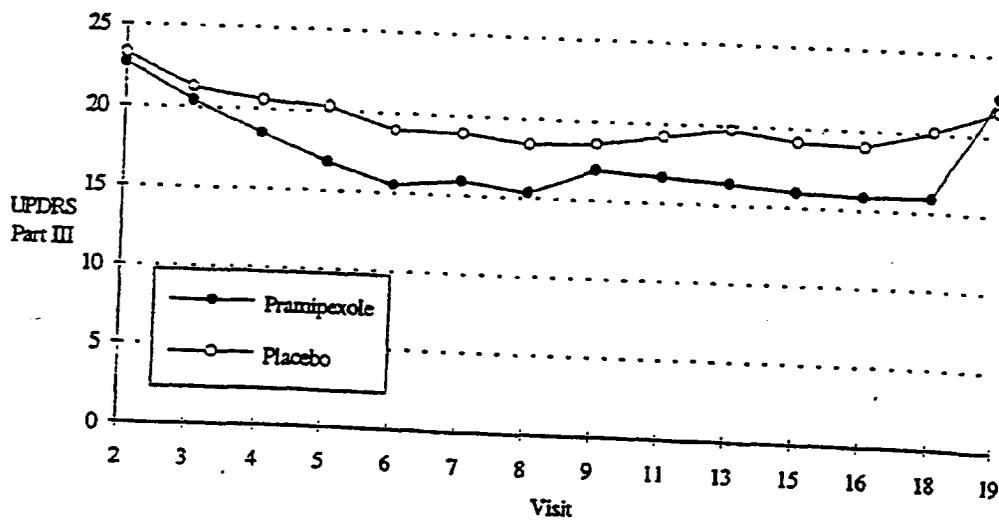


Average UPDRS Part II 'off' and 'on' Means by Visit.

Observed Cases Analysis

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FIGURE 4



UPDRS Part III Means by Visit.

Observed Cases Analysis

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TABLE 19

Unadjusted Means, Standard Deviations, and Sample Sizes for Average Percentage of 'off' Period Time by Visit.

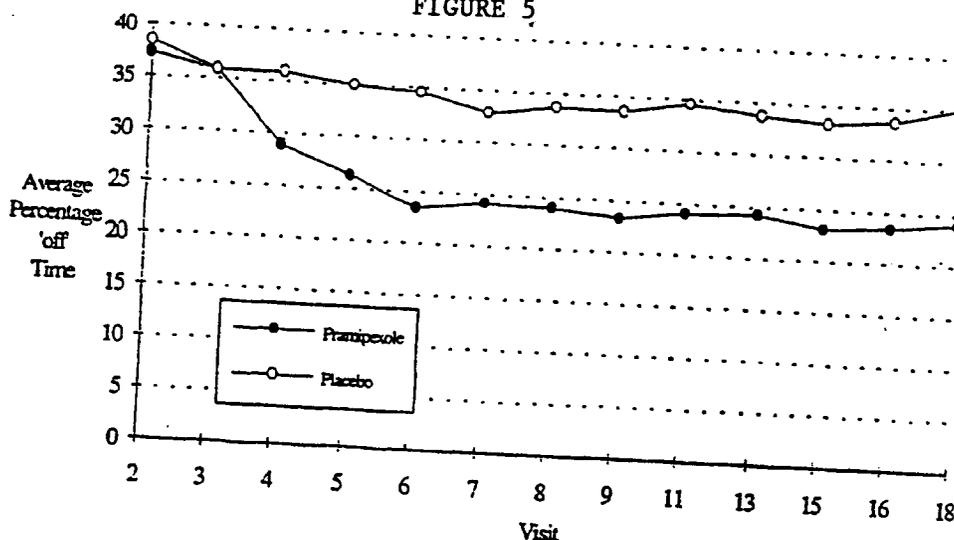
Last Observation Carried Forward Analysis

Group	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Pramipexole:							
Mean =	37.20	35.88	28.85	26.24	23.46	24.22	24.02
S.D. =	19.91	21.06	20.42	20.43	20.43	22.32	21.59
n =	173	173	173	173	173	173	173
Placebo:							
Mean =	38.28	35.91	35.88	34.92	34.54	32.79	33.61
S.D. =	20.35	18.88	19.80	20.71	21.20	21.07	21.64
n =	172	172	172	172	172	172	172

Group	Visit 9	Visit 11	Visit 13	Visit 15	Visit 16	Visit 18
Pramipexole:						
Mean =	23.31	24.06	24.24	23.08	23.39	24.01
S.D. =	21.46	22.75	22.28	21.25	20.79	22.45
n =	173	173	173	173	173	173
Placebo:						
Mean =	33.48	34.55	33.70	33.18	33.59	35.13
S.D. =	21.99	22.32	22.76	23.69	24.63	24.24
n =	172	172	172	172	172	172

Source Data: Appendix 15.9.2 STATDOC 4.5.1

FIGURE 5



Average Percentage 'off' Time by Visit.
Last Observation Carried Forward Analysis

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TABLE 20

Protocol M/1730/0004
 UPDRS I-III TOTAL SCORE+
 BY L-DEPRENYL AND ANTICHOLINERGIC USE AT BASELINE
 MEAN CHANGE FROM BASELINE TO ENDPOINTS - ALL PATIENTS

L-Deprenyl	Yes	N	PPX 1.5 mg	PPX 3.0 mg	PPX 4.5 mg	PPX 6.0 mg	Placebo
			30	33	36	32	30
		Mean Baseline	27.9	26.7	25.2	29.9	25.3
		Mean Endpoint	20.3	19.2	19.1	24.3	23.4
		Mean Change	-7.6	-7.5	-6.1	-5.7	-1.9
		S.E.	1.32	0.98	0.99	1.17	1.49
	No	N	23	17	18	23	21
		Mean Baseline	29.3	31.3	31.5	37.0	33.6
		Mean Endpoint	24.5	28.4	24.0	28.0	34.2
		Mean Change	-4.8	-2.9	-7.5	-9.0	0.6
		S.E.	2.28	1.66	2.71	1.98	2.24
Anticholinergic	Yes	N	35	37	41	37	34
		Mean Baseline	28.2	27.1	26.8	31.5	25.3
		Mean Endpoint	20.9	20.5	20.3	25.3	24.0
		Mean Change	-7.4	-6.6	-6.5	-6.2	-1.3
		S.E.	1.26	0.99	0.91	1.14	1.37
	No	N	16	13	13	18	17
		Mean Baseline	29.0	31.5	29.1	35.7	35.5
		Mean Endpoint	24.5	27.6	22.3	26.9	35.5
		Mean Change	-4.5	-3.9	-6.8	-8.8	0.0
		S.E.	2.71	2.04	3.71	2.35	2.71

+ Sum of the 31 components of UPDRS Parts I, II and III (Range = 0 - 176).
 § Values taken at the baseline visit, Visit 2 (Week 0).
 §§ Last visit, prior to dose-reduction.
 Treatment groups are classified by assigned (target) dose.

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TABLE 21

UPDRS Part II Average of 'off' and 'on' Periods Change from Baseline to Final for L-Deprenyl Users Only and All Patients.

Last Observation Carried Forward Analysis

	Intent-to-Treat Data Set	L-Deprenyl Users
Pramipexole	-2.72 n = 179	-2.97 n = 97
Placebo	-0.47 n = 171	-0.82 n = 93
p-value	≤0.0001	0.0005

UPDRS Part III Change from Baseline to Final for L-Deprenyl Users Only and All Patients.

Last Observation Carried Forward Analysis

	Intent-to-Treat Data Set	L-Deprenyl Users
Pramipexole	-5.64 n = 179	-6.82 n = 97
Placebo	-2.79 n = 171	-3.06 n = 93
p-value	0.01	0.01