2. UPDRS Part II

Sponsor's Figure 9.3.1.1.1:1 (next page) shows the average Part II scores (off and on means) by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

Sponsor's Figure 13.2.1 (next page) shows the observed case results for the same comparison. Page 68 of the study report states that 37 of 69 patients who dropped out did not return for evaluation at what would have been their visit 18. These 37 patients are not part of the OC analysis.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant. Consistency across other analyses of the same outcome variable can be seen below:

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)	OC Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-2.7	-2.8	-57	-54
Placebo	-0.5	-0.5	-18	-17
p-value	$\leq$ 0.0001	$\leq$ 0.0001	$\leq$ 0.0001	$\leq$ 0.0001

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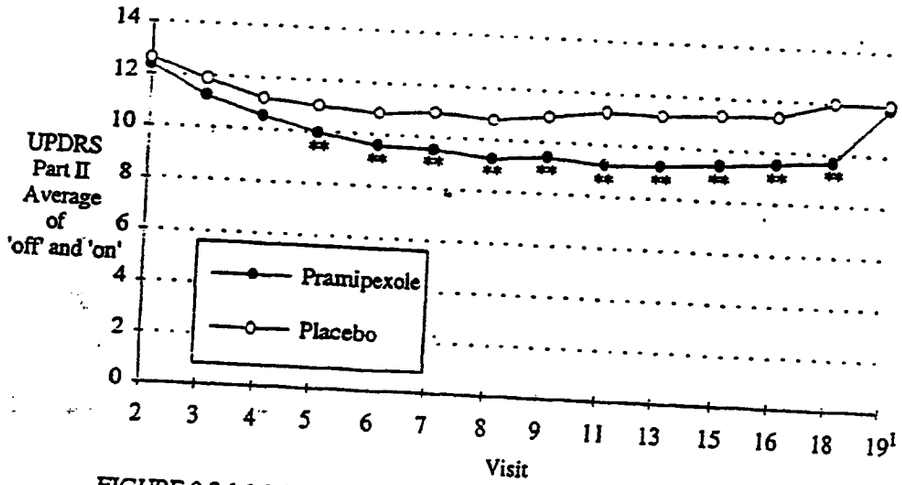


FIGURE 9.3.1.1.1:1 Average UPDRS Part II 'off' and 'on' Means by Visit.
Last Observation Carried Forward Analysis

Source Data: TABLE 9.3.1.1.1:1
* p ≤ 0.05 ** p ≤ 0.01 [1] Observed Cases Analysis Only

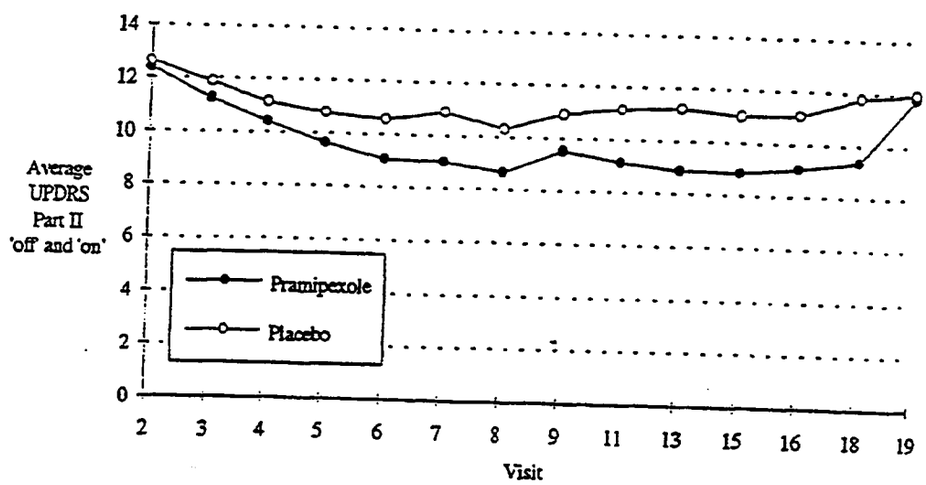
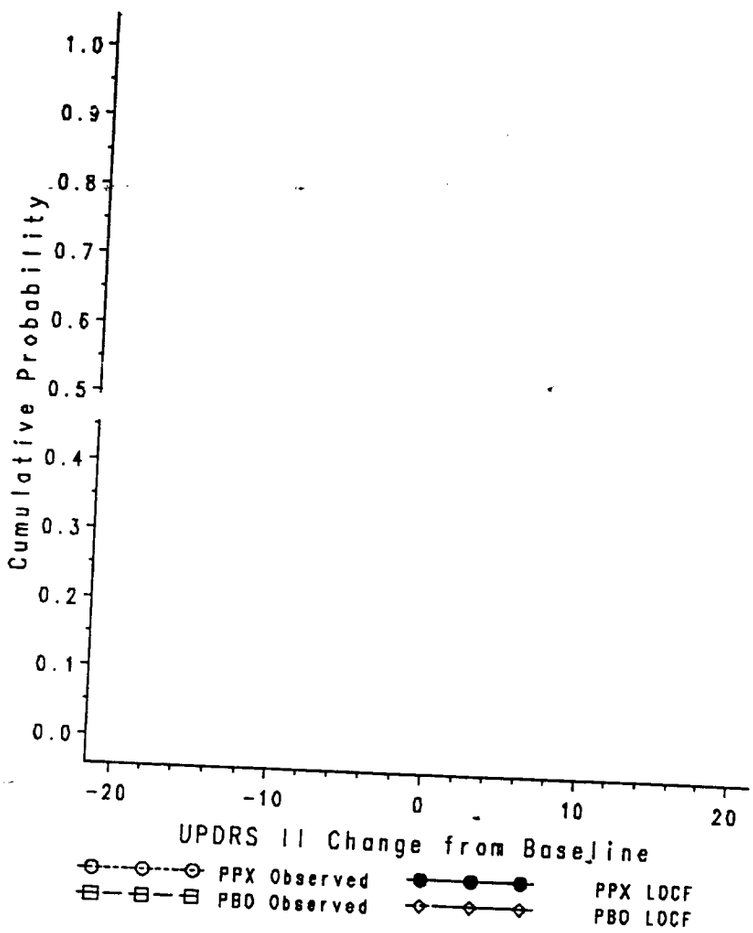


FIGURE 13.2.1 Average UPDRS Part II 'off' and 'on' Means by Visit.

Observed Cases Analysis

Ogive Curve of UPDRS II Change from Baseline -- M/2730/0010



Sponsor's Figure 9.3.1.2.2:1 (next page) shows the average Part II scores (on only) by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.1:1 (next page) shows the average Part II scores (off only) by visit for the two treatment groups.

For Part II, on, the difference in the treatment groups came from a number of components, with the largest components being: Turning in Bed, Cutting Food, and Hygiene.

For Part II, off, the difference in the treatment groups came from a number of components, with the largest components being: Freezing When Walking, Cutting Food, Walking, Hygiene, Turning in Bed, and Tremor.

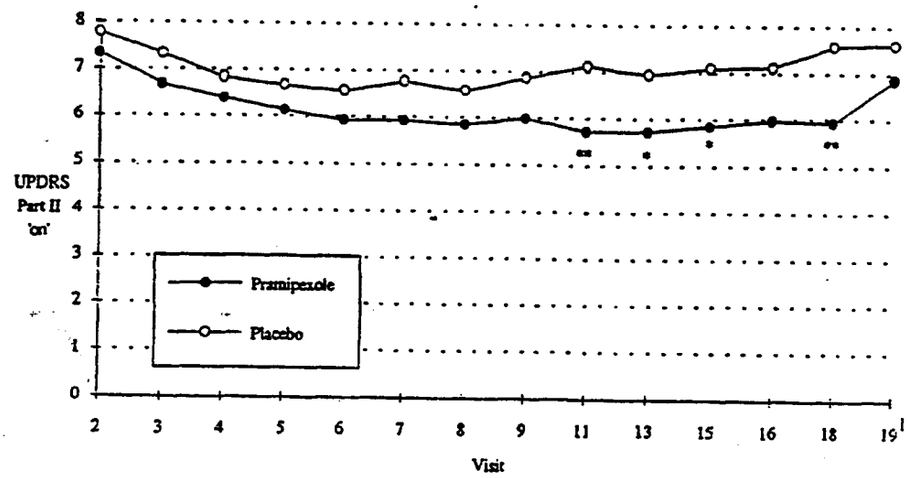


FIGURE 9.3.1.2.2:1 UPDRS Part II 'on' Means by Visit.

Last Observation Carried Forward Analysis

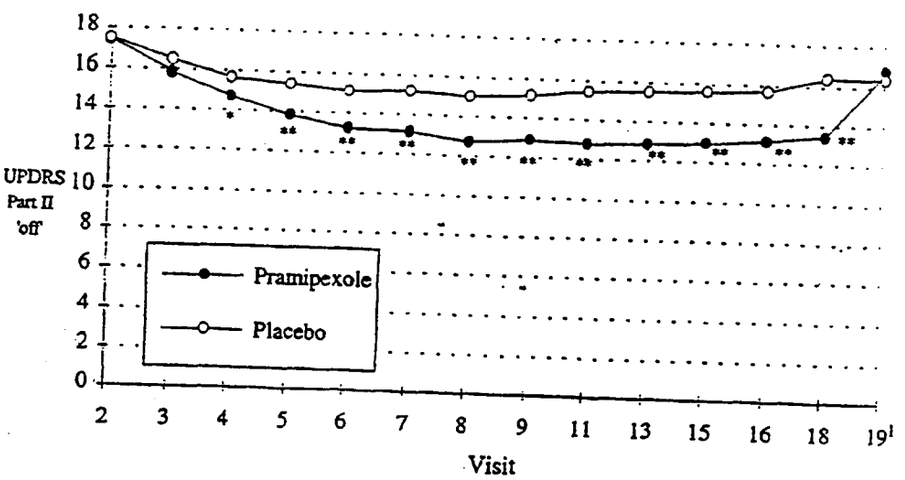


FIGURE 9.3.1.2.1:1 UPDRS Part II 'off' Means by Visit.

Last Observation Carried Forward Analysis

3. UPDRS Part III

Sponsor's Figure 9.3.1.1.2:1 (next page) shows the average Part III scores by visit for the two treatment groups. The sponsor provided cumulative distribution functions for the treatment groups and these are shown on the page after that.

Sponsor's Figure 13.2.2 (next page) shows the observed case results for the same comparison.

The protocol specified analysis was a comparison between treatment groups of change from baseline to final maintenance visit (LOCF), adjusted by center and center-by-treatment interaction. The results of this analysis were highly statistically significant. Consistency across other analyses of the same outcome variable can be seen below:

	LOCF Change from Baseline to Final Maintenance Visit	OC Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)	OC Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-5.6	-5.7	-114	-126
Placebo	-2.8	-3.7	-64	-75
p-value	0.01	0.08	0.01	0.02

For Part III, the difference in the treatment groups came from a number of components, with the largest components being: Leg Agility, Finger Taps, Rigidity, and Hand Movements.

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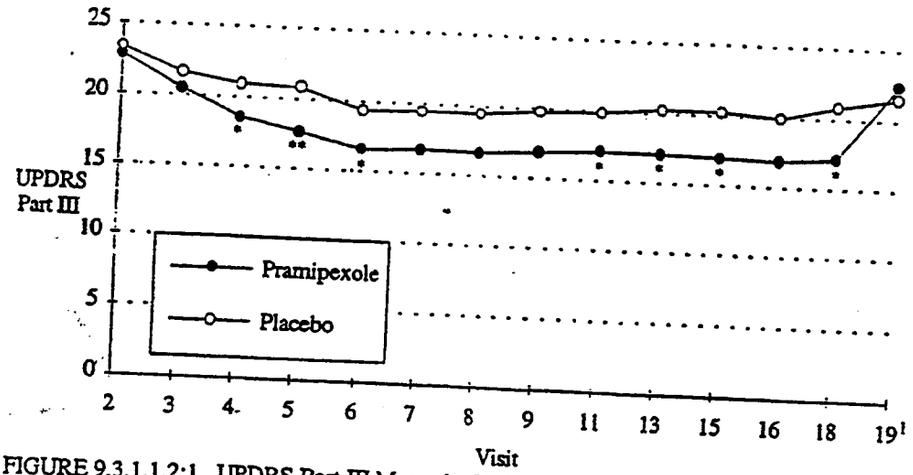


FIGURE 9.3.1.1.2:1 UPDRS Part III Means by Visit.

Last Observation Carried Forward Analysis

Source Data: TABLE 9.3.1.1.2:1

[1] Observed Cases Analysis Only

* $p \leq 0.05$ ** $p \leq 0.01$

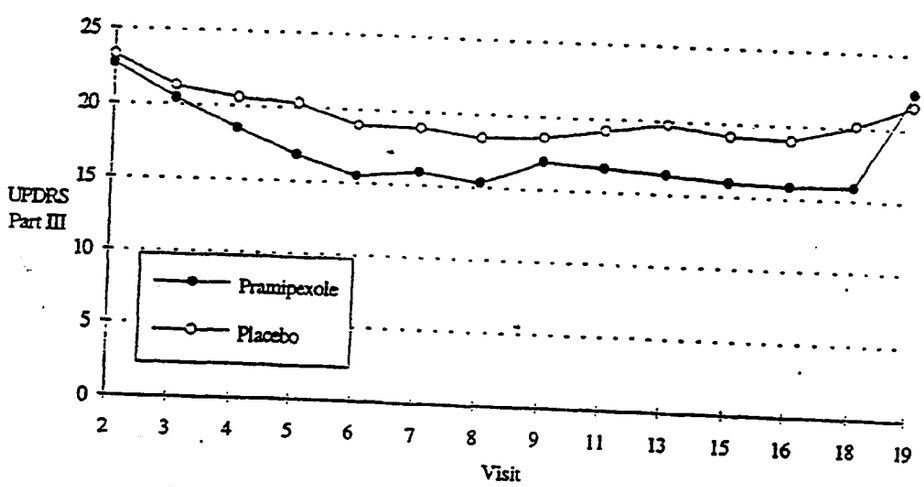
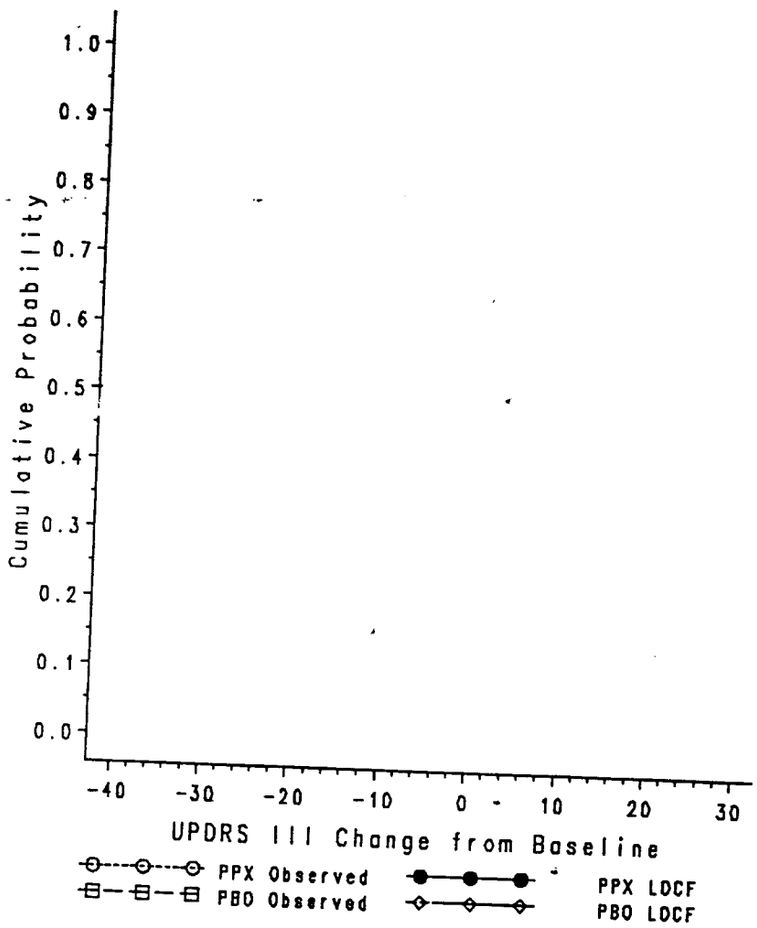


FIGURE 13.2.2 UPDRS Part III Means by Visit.

Observed Cases Analysis

Ogive Curve of UPDRS III Change from Baseline -- M/2730/0010



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4. UPDRS Part I

Sponsor's Figure 9.3.1.2.10:1 (next page) shows the average Part I scores by visit for the two treatment groups. No real difference between groups is seen.

5. UPDRS Part IV

Sponsor's Figure 9.3.1.2.11:1 (next page) shows the average Part IV scores by visit for the two treatment groups.

6. Parkinson Dyskinesia Scale

Sponsor's Figure 9.3.1.2.12:1 (next page) shows the average PDS scores by visit for the two treatment groups. There is an interesting peak in scores for pramipexole patients at visit 9. Note that the scores that contribute to this visit average score represent a mix of experience on a new higher dose for patients who were increased to the maximum allowed dose at visit 8 as well as experience on a stable dose for patients who did not reach the highest dose and were moved to visit 9 after skipping intermediate visits. This might tell us that the highest dose caused a significant increase in dyskinesia in those patients that achieved that dose, an increase that was diluted out by the scores of patients that did not go to that level. Presumably, patients could have the dose lowered at visit 9 back down to the next highest dose.

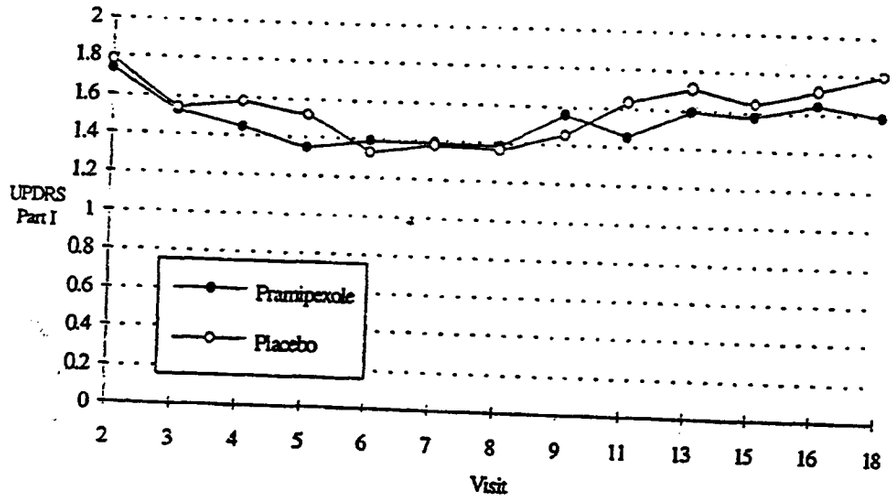

FIGURE 9.3.1.2.10:1 UPDRS Part I Means by Visit.

Last Observation Carried Forward Analysis

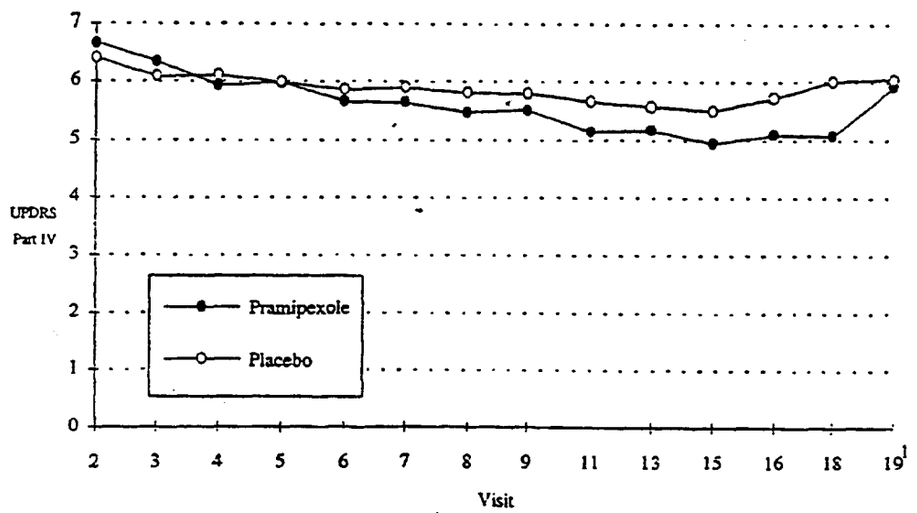

FIGURE 9.3.1.2.11:1 UPDRS Part IV Means by Visit.

Last Observation Carried Forward Analysis

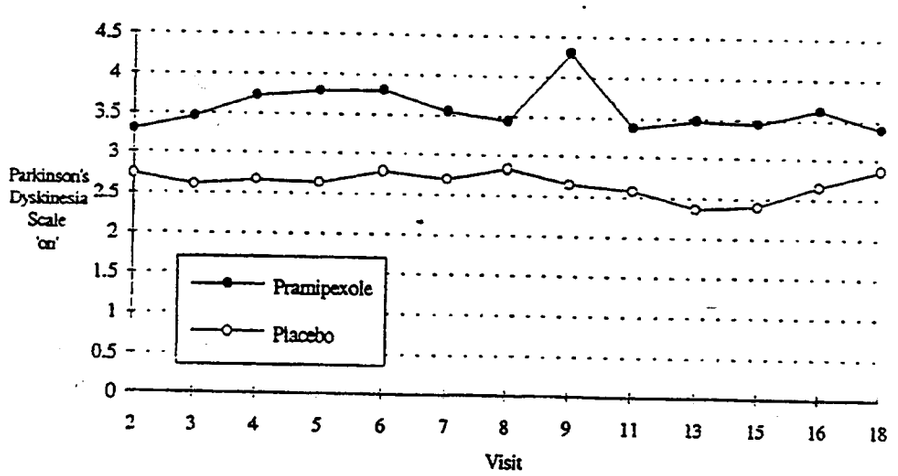

FIGURE 9.3.1.2.12:1 Parkinson Dyskinesia Scale 'on' Means by Visit.

Last Observation Carried Forward Analysis

7. Modified Schwab-England Disability Scale

This scale was completed for both the on and off periods.

Sponsor's Figure 9.3.1.2.6:1 (next page) shows the average "off" scores by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.7:1 (next page) shows the average "on" scores by visit for the two treatment groups.

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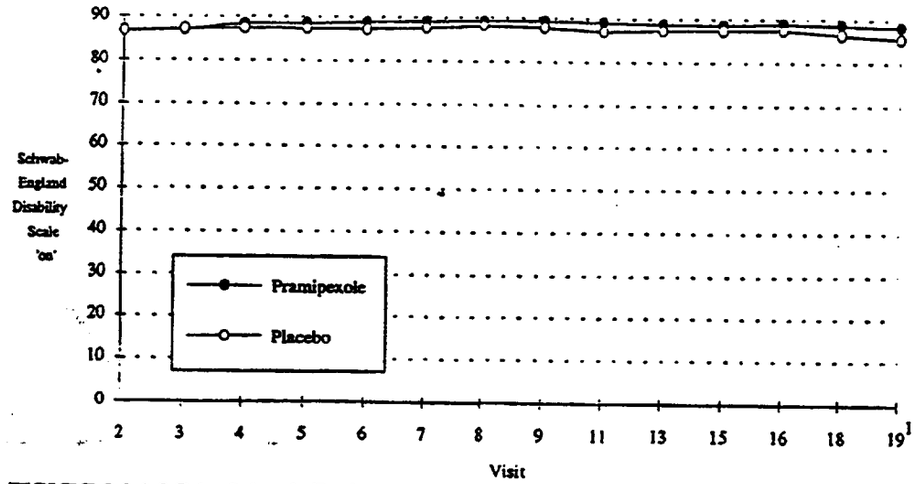

FIGURE 9.3.1.2.7:1 Schwab-England Disability Scale 'on' Means by Visit.

Last Observation Carried Forward Analysis

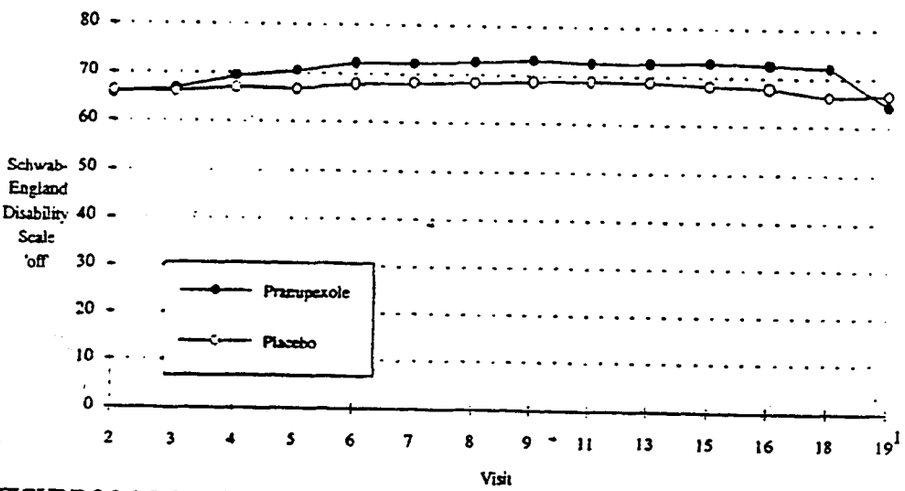

FIGURE 9.3.1.2.6:1 Schwab-England Disability Scale 'off' Means by Visit.

Last Observation Carried Forward Analysis

8. Modified Hoehn and Yahr Scale

This scale was completed for both the on and off periods.

Sponsor's Figure 9.3.1.2.8:1 (next page) shows the average "off" scores by visit for the two treatment groups.

Sponsor's Figure 9.3.1.2.9:1 (next page) shows the average "on" scores by visit for the two treatment groups.

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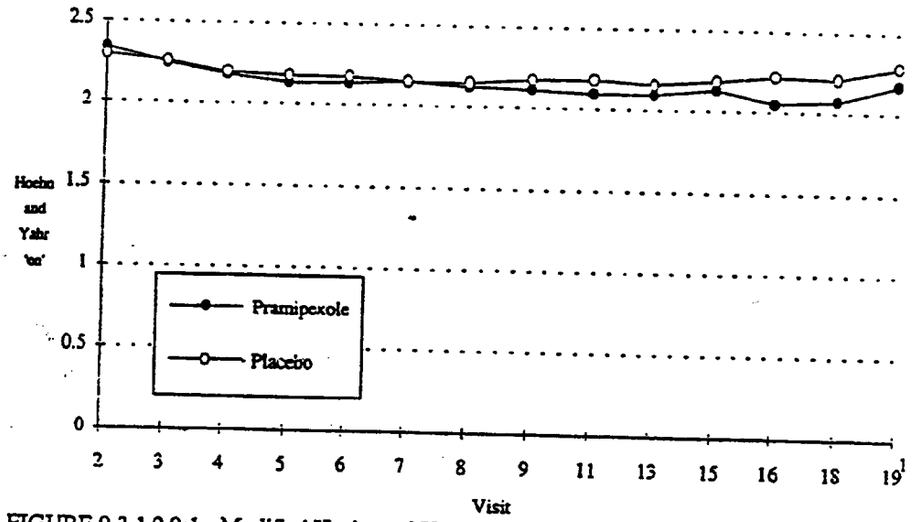

FIGURE 9.3.1.2.9:1 Modified Hoehn and Yahr Scale 'on' Means by Visit.
Last Observation Carried Forward Analysis

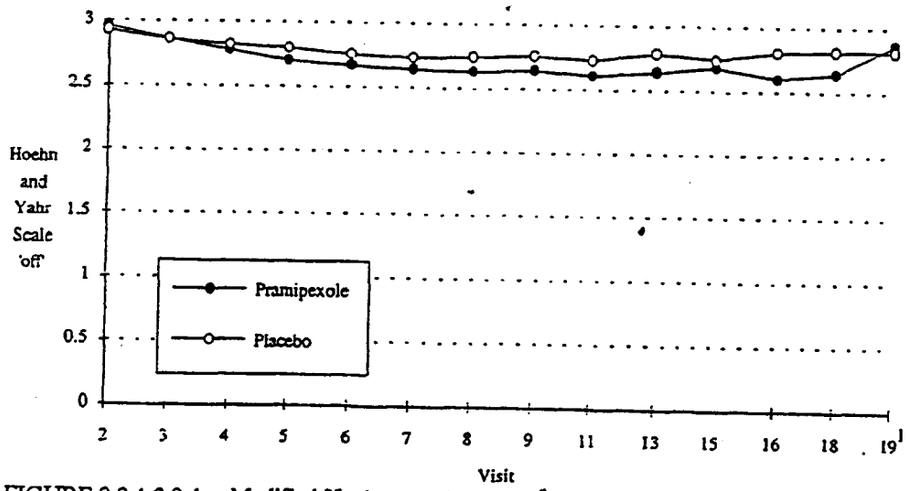

FIGURE 9.3.1.2.8:1 Modified Hoehn and Yahr Scale 'off' Means by Visit.
Last Observation Carried Forward Analysis

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9. Timed Walking Test

Sponsor's Figure 9.3.1.2.13:1 (next page) shows the average times by visit for the two treatment groups. The curves cross several times, with no overall differences emerging.

10. Average Severity Level of Off Periods From Patient Diaries

Sponsor's Figure 9.3.1.2.4:1 (next page) shows the average severity score by visit for the two treatment groups.

Dosage of L-Dopa, Other Concomitant Anti-Parkinson's Drugs

By protocol, during the maintenance phase, the dose of L-dopa could be adjusted downward if dyskinesias, hallucinations, or psychiatric side effects developed.

Dosage data on L-dopa was collected at each visit, but the sponsor states (without further explanation on p95 of the study report) that problems arose with interpreting CRF data on dosage. "Ultimately it was decided that the CRFs for baseline and final maintenance visit had to be individually reviewed by a sponsor's medical monitor. This review was conducted while the treatment code was still blinded. Because this review was very time consuming, only data from these two visits were collected."

Sponsor's Table 9.3.1.2.5:1 (next page) gives the baseline visit mean dosage, the final maintenance visit mean dosage, and the unadjusted and adjusted change from baseline to final maintenance visit. The pramipexole group reduced L-dopa dosage by 25% while the placebo group reduced dosage by 6% ($p \leq 0.0001$).

For each visit during the study, the CRF contained a box that the investigator could check if there had been no change in L-dopa dosage since the previous visit. It is informative to know the proportion of patients in each treatment group that had no change in L-dopa dosage throughout the study: 24% pramipexole, 46% placebo. Given the protocol-specified rules for changing L-dopa dose, the different proportions of patients requiring L-dopa dosage changes would be consistent with the 19% higher frequency of dyskinesias and the 15% higher frequency of

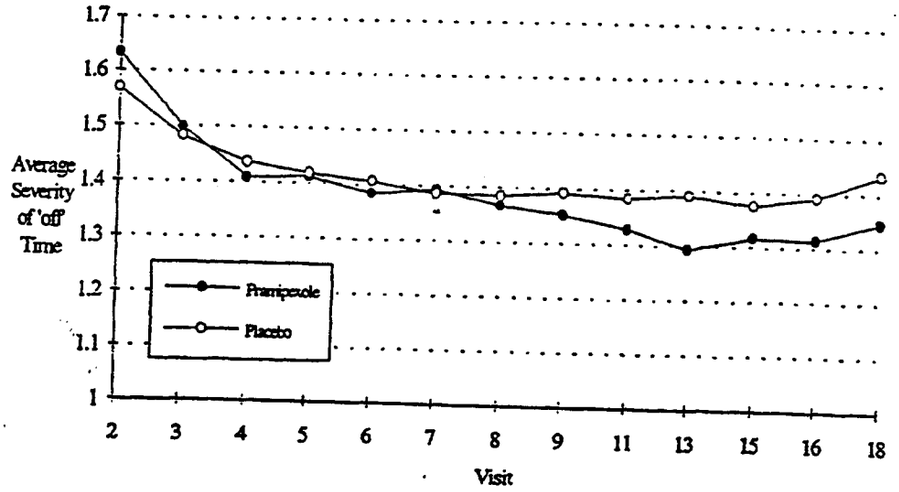

FIGURE 9.3.1.2.4:1 Average Severity of 'off' Time by Visit.

Last Observation Carried Forward Analysis

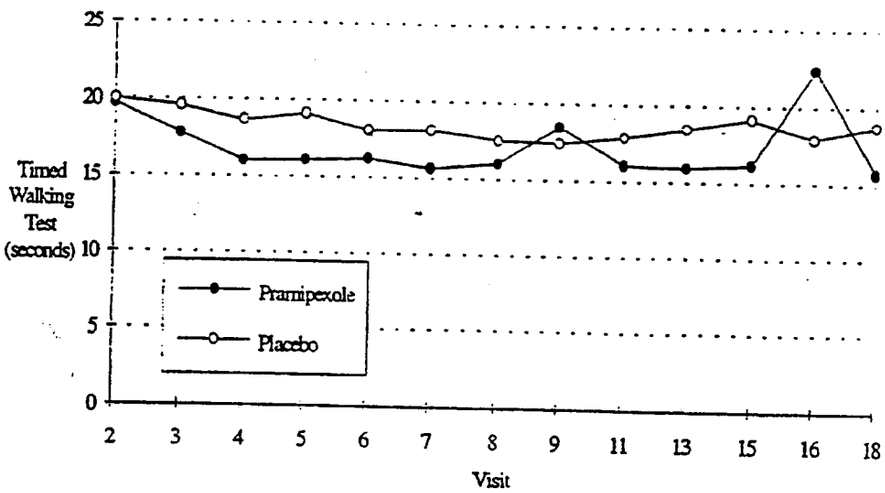

FIGURE 9.3.1.2.13:1 Timed Walking Test Means by Visit.

Last Observation Carried Forward Analysis

TABLE 9.3.1.2.5:1 Levodopa Dose (mg) Mean (S.D.) Change from Baseline.

Last Observation Carried Forward Analysis

	Baseline	Final Maintenance Visit	Unadjusted Change from Baseline to Final Visit on Maintenance	Adjusted[1] Change from Baseline to Final Visit on Maintenance
Pramipexole n = 179	843.37 (578.86)	633.89 (540.91)	-209.48 (272.55)	-229.68
Placebo n = 172	819.19 (466.08)	773.98 (453.72)	-45.20 (115.86)	-43.20
p-value				≤ 0.0001

Source Data: Appendix 15.9.2 STATDOC 4.7.1 & 4.7.2

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

hallucinations in the pramipexole group.

Changes in deprenyl, anticholinergic, and amantadine dosing during the trial were not allowed by protocol. Any changes should have been reported as protocol violations. No protocol violations on this issue are recorded in the study report.

In the September 27 submission, the sponsor reported that small numbers of patients did have their dosages of these drugs changed during the trial. However, the numbers are so small as to be insignificant.

The importance of the above questions should be obvious. All alternative explanations for a favorable effect in the pramipexole group must be ruled out.

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ON ORIGINAL

Table A4
Number of patients received Amantadine, Deprenyl, and Anti-Cholinergics
M/2730/0010

		Pramipexole	Placebo
	Total N randomized	181	178
Amantadine	Took Drug During Study*	33	25
	Stopped Drug During Study	1	0
	Increased Dosage	0	2
	Decreased Dosage	4	1
	Stopped/Restarted Drug	1	0
	No Change	27	22
Deprenyl	Took Drug During Study*	103	93
	Stopped Drug During Study	4	0
	Increased Dosage	1	0
	Decreased Dosage	5	2
	Stopped/Restarted Drug	1	1
	No Change	92	90
Anti-Cholinergics	Took Drug During Study*	25	26
	Stopped Drug During Study	0	0
	Increased Dosage	1	4
	Decreased Dosage	5	6
	Stopped/Restarted Drug	1	0
	No Change	18	16

* Not include patients who were on such drugs but stopped them prior to enrollment in the study, also does not include patients who started the drugs after the end of the maintenance dose phase.

D. Plasma Levels

1. Plasma pramipexole levels were collected in order to assess mean population PK parameters and their variance in this population. The results of this analysis are to be summarized in a separate report.

2. Plasma levels of concomitant L-dopa, deprenyl, and anticholinergics were not measured during the conduct of this trial.

Only 26 patients in the pramipexole group were using anticholinergic medications. 97 patients in the pramipexole group were using deprenyl. By design, all patients were using L-dopa.

E. Adverse Events

Sponsor's Table 11:1 shows the AEs with an incidence of 10% or greater in the pramipexole group. Only dyskinesia and hallucinations were statistically significantly different between the two treatment groups. Dose reductions of study medication controlled most cases of dyskinesia and hallucination.

Most AEs were typical of dopamine agonists and were mild to moderate in severity.

One pramipexole patient experienced repeated elevations of LFTs and was discontinued. Later rechallenge was tolerated. When comparing pramipexole and placebo patients with respect to lab change-from-baseline, statistically significant differences between the treatment groups were noted for: SGOT, SGPT, CPK, and LDH. The sponsor believes all these lab changes could be explained by pramipexole induced dyskinesias.

TABLE 11:1 **Summary of the Most Common Adverse Events for the Pramipexole and Placebo Treatment Groups**

	Pramipexole N=181		Placebo N=179		
	Number	Percent	Number	Percent	P Value
Dyskinesia	113	62	77	43	0.0003
Asymptomatic orthostatic hypotension	102	56	108	60	NS
Dizziness	75	41	67	37	NS
Parkinsonism aggravated	64	35	61	34	NS
Pain	62	34	60	34	NS
Insomnia	51	28	49	27	NS
Nausea	44	24	50	28	NS
Hallucinations	38	21	10	6	<0.0001
Symptomatic orthostatic hypotension	30	17	23	13	NS
Confusion	23	13	18	10	NS
Constipation	23	13	22	12	NS
Upper respiratory tract infection	21	12	29	16	NS
Somnolence	19	11	16	9	NS

Source Data: TABLE 15.1.16

F. Conclusions

Pramipexole-treated patients, on average, saw a larger change-from-baseline on Part II of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was small, but highly statistically significant.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline on Part III of the UPDRS than their counterparts treated with placebo. This difference in average change-from-baseline was again small, but highly statistically significant.

The protocol called for a statistically significant result on each of these outcome measures (a dual outcome) in order for a positive result to be declared for the trial as a whole.

Pramipexole-treated patients, on average, also saw a larger change-from-baseline in percentage of waking hours spent in the "off" state compared to their counterparts treated with placebo. The shift from "off" could have been to "on with dyskinesia" and not simply to "on." This issue could be resolved by patient diaries, but not by CRFs. The sponsor has not shown an interest in pursuing this further.

The 3 improvements above came at a cost of more hallucinations and more dyskinesias as demonstrated in AE listings. In the UPDRS scale, hallucinations are only a component of Part I and dyskinesias are only a component of Part IV. The pertinent items from Parts I and IV for hallucinations and dyskinesias are not analyzed separately.

In short, Part III of the UPDRS may be a good scale for measuring Parkinson's Disease, but it may not be a good scale for measuring the patient population under study here: patients with motor fluctuations after 2-3 years of L-dopa therapy. Dyskinesias are a part of the motor fluctuations and are not included in Part III. The optimal state for these patients probably represents a fine balance in their dopaminergic states. Each patient will have a preference toward one end of the spectrum: too much dopaminergic stimulation with hallucinations, dyskinesias, but better mobility versus too little dopaminergic stimulation with decreased mobility. The labeling should clarify the trade off between the two states.

There is one last comment, more for the record than anything else. That is, the evidence accrued in this study, viewed in isolation, provides an alternate explanation for better performance in the pramipexole group than the use of pramipexole. To assume that pramipexole explains the better performance, one has to assume (reasonably I think) that chronic L-dopa in this patient population does not **cause** the "off" state and does not **worsen** performance on Parts II and III of the UPDRS. If L-dopa did these things, then the mere fact that dosage of L-dopa was reduced more in one group than the other could explain the better performance in one group. The prevalent theory, however, holds that the "on-off" phenomena and the decreased performance that occur after chronic use of L-dopa are all due to **decreased responsiveness to L-dopa.** It would then follow logically that the decreased average dose of L-dopa seen in one treatment group would serve to worsen, not improve that group's outcomes; improvement in that group could then be attributed to the addition of pramipexole (c.f. drug holidays in Parkinson's disease).

In short, pramipexole **substituted for L-dopa** resulted in less off time, better scores on UPDRS Parts II and III, more hallucinations, and more dyskinesias than when placebo was added to L-dopa.

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TR No.: 9158-95-023

Boehringer Ingelheim Pharmaceuticals, Inc.
Trial No.: 248.320

RATING SCALES Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
		2			1001	19

The same person should conduct each part of this evaluation throughout the trial.

PARKINSON DYSKINESIA SCALE (This exam MUST be completed when the patient is in an 'on' period)

This examination should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

TIME OF EXAMINATION: ____ : ____ (24-hour clocktime) RATER'S INITIALS (3): ___ ___ ___

INTENSITY OF DYSKINESIA DURING 'ON' PERIOD:
Rate the patient's present intensity of dyskinesia during an 'on' period by using the following scale. If the patient is in an 'off' period, wait until the patient enters an 'on' period.

0 = Normal
1 = Intermittent
2 = Generalized, mild but continuous, may not be obvious to untrained observer
3 = Moderate, generalized, definitely noticeable to untrained observer
4 = Incapacitating

	0	1	2	3	4
Head	☐	☐	☐	☐	☐
RUE	☐	☐	☐	☐	☐
LUE	☐	☐	☐	☐	☐
RLE	☐	☐	☐	☐	☐
LLE	☐	☐	☐	☐	☐
Trunk	☐	☐	☐	☐	☐

MODIFIED SCHWAB-ENGLAND DISABILITY SCALE RATER'S INITIALS (3): ___ ___ ___

Rate the patient's best 'on' period and worst 'off' period during the past week by checking one box under each column.

ON	OFF	
☐	☐	100% - Completely independent. Able to do all chores without slowness, difficulty, or impairment. Essentially normal. Unaware of any difficulty.
☐	☐	90% - Completely independent. Able to do all chores with some degree of slowness, difficulty, and impairment. Might take twice as long. Beginning to be aware of difficulty.
☐	☐	80% - Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.
☐	☐	70% - Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.
☐	☐	60% - Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.
☐	☐	50% - More dependent. Help with half, slower, etc. Difficulty with everything.
☐	☐	40% - Very dependent. Can assist with all chores, but few alone.
☐	☐	30% - With effort, now and then does a few chores alone or begins alone. Much help needed.
☐	☐	20% - Nothing alone. Can be a slight help with some chores. Severe invalid.
☐	☐	10% - Totally dependent, helpless, complete invalid.
☐	☐	0% - Vegetative functions such as swallowing, bladder, and bowel functions are not functioning. Bedridden.

MODIFIED HOEHN AND YAHR SCALE RATER'S INITIALS (3): ___ ___ ___

Indicate the patient's Parkinson stage for both 'on' and 'off' periods by checking one box for 'on' and one box for 'off' below.

STAGE	ON	OFF	
0	☐	☐	No signs of disease
1	☐	☐	Unilateral disease
1.5	☐	☐	Unilateral plus axial involvement
2	☐	☐	Bilateral disease, without impairment of balance
2.5	☐	☐	Mild bilateral disease, with recovery on pull test
3	☐	☐	Mild to moderate bilateral disease; some postural instability; physically independent
4	☐	☐	Severe disability; still able to walk or stand unassisted
5	☐	☐	Wheelchair bound or bedridden unless aided

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CANARY COPY: INVESTIGATOR

TR No.: 9158-95-023

Boehringer Ingelheim Pharmaceuticals, Inc.
Trial No.: 248.320

TREATMENT EVALUATION

Pramipexole 00679A – M2730/0010

PATIENT INITIALS (3)	DATE OF VISIT (month/day/year)	VISIT	INVEST NO	SHEET NO	PATIENT NO	PAGE
☐☐☐	☐☐☐☐☐☐	2			1001	20

Last Dose	Date (month/day/year)	Time (24-hour clocktime)	Dose (e.g. 25 / 100)	Number of Tabs / Caps
Decarboxylase Inhibitor / Levodopa				

TIMED WALKING TEST TIME OF EXAMINATION: ___:___ (24-hour clocktime)

(This exam MUST be completed when the patient is in an 'on' period)

The Timed Walking Test should be completed approximately two to three hours following a dose of decarboxylase inhibitor / levodopa therapy but prior to the initial dose of trial drug.

Record the time needed to complete the test to the nearest whole second.

Time to complete: _____min. _____sec.

Was the use of a walker required? 0☐No 1☐Yes

Completed test within 10 minutes? 0☐No 1☐Yes

Time Interval	24-hour Clocktime	SUPINE VITAL SIGNS (after 5 minutes of quiet rest) Systolic/Diastolic BP (mm Hg)	Pulse (bpm)	STANDING VITAL SIGNS (after 1 minute standing) Systolic/Diastolic BP (mm Hg)	Pulse (bpm)	ORTHOSTATIC HYPOTENSION* (refer to protocol for definition)
Pre-Dose	___:___	/		/		0☐None 1☐Symptomatic* 2☐Asymptomatic*
Administer Trial Medication	___:___	Administer the contents of the first blister for Dose 1.				
2 Hours after Administration	___:___	/		/		0☐None 1☐Symptomatic* 2☐Asymptomatic*

* If orthostatic hypotension is present, record on the "Adverse Event Report" form. Indicate symptomatic or asymptomatic. If symptomatic, record specific symptoms.

Appendix D

Daily Patient Records

The patient will record when "on-off" disabilities occur during waking hours. "On" periods are periods with good motor function, while "off" periods are periods when patients move slowly or not at all. In addition to recording the specific times of on and off periods during the day, patients should also score the degree of disability during "off" periods using the following 4-point scale:

1. (mild slowness, stiffness, or resting tremor)

2. (moderate slowness, stiffness, or resting tremor, but remaining functionally independent)

3. (severe disability, the patient requiring some help in several activities)

4. (immobile, severely incapacitated and totally dependent on others)

"On" periods with dyskinesia (i.e., when patients are able to move, but are troubled by involuntary or uninentional movements) will also recorded.

The patient will be asked to record activity for one-hour periods during waking hours. If more than one activity applies (e.g., "on" and "on" with dyskinesia), record the activity which predominated during the one hour period.

The number of hours off per day divided by the total number of waking hours will be averaged over each week of assessment and recorded on case report forms. In addition, the disability score during "off" periods per day will also be averaged over each week of assessment. "On-off" periods for at least 2 full days prior to the next clinic visit should be recorded by the patient within the diary.

Guardians, family members, or nursing personnel, etc., may assist the patient in completing the daily patient record. If there are errors, inconsistencies, discrepancies, or missing information, these should be resolved at the time of the clinic visit.

TR No.: 9158-95-023

DAILY PATIENT RECORD			SND 919 00655
PATIENT INITIALS (3)	DATE RECORD COMPLETED (month/day/year)	VISIT (dispensed)	PATIENT NUMBER
		2	

INSTRUCTIONS:

Circle the appropriate description for each one-hour period during the day. If more than one applies, circle the clinical status description which predominated (lasted 30 minutes or more) during each period.

ON	= Good motor function
ON WITH DYSKINESIAS	= Able to move, but troubled by involuntary or unintentional movements
OFF	= Able to move slowly or not at all.

For each 'OFF' period, check the highest degree of severity experienced. Four degrees of severity are defined below:

1	=	mild slowness, stiffness, or resting tremor
2	=	moderate slowness, stiffness, or resting tremor, but remaining functionally independent
3	=	severe disability, requiring assistance in several activities
4	=	immobile, severely incapacitated, and totally dependent on others

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TIME INTERVAL	CLINICAL STATUS				Severity of "OFF" period			
					1	2	3	4
MIDNIGHT - 1 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
1 AM - 2 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
2 AM - 3 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
3 AM - 4 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
4 AM - 5 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
5 AM - 6 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
6 AM - 7 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
7 AM - 8 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
8 AM - 9 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
9 AM - 10 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
10 AM - 11 AM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
11 AM - 12 NOON	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
12 NOON - 1 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
1 PM - 2 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
2 PM - 3 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
3 PM - 4 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
4 PM - 5 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
5 PM - 6 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
6 PM - 7 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
7 PM - 8 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
8 PM - 9 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
9 PM - 10 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
10 PM - 11 PM	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
11 PM - 12 MIDNIGHT	ASLEEP	ON	ON WITH DYSKINESIAS	OFF				
FOR OFFICE USE ONLY								
TOTAL NUMBER OF HOURS	24 - _____ asleep = _____ waking hrs. -							

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Adler, Charles H, M.D., Ph.D. Assistant Professor Mayo Clinic Scottsdale 13400 East Shea Boulevard Scottsdale, AZ 85259	13
Comella, Cynthia, M.D. Dept. of Neurological Sciences Rush Medical College Rush-Presbyterian St. Luke's Medical Center 1725 West Harrison Chicago, IL 60612	12
Curran, Terry, M.D. (6/24/93-12/12/93) Goodridge, Alan, M.D. (12/13/93-present) Division of Neurology The General Hospital Health Sciences Centre 300 Prince Philip Drive St. John's Newfoundland A1B 3V6	12
Eidelman, Benjamin, M.D. Acting Chairman, Dept. of Neurology University of Pittsburgh 337 East Scaife Hall Pittsburgh, PA 15261	11
Factor, Stewart A, D.O. Assistant Professor of Neurology Dept. of Neurology Albany Medical Center New Scotland Avenue Albany, NY 12208	20
Fazzini, Enrico, D.O. New York University Medical Center 530 First Avenue, Suite 9Q New York, NY 10016	20
Friedman, Joseph, M.D. Department of Neurology Roger Williams General Hospital 825 Chalkstone Avenue Providence, RI 02908	8

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Golbe, Lawrence I, M.D. Clinical Academic Building 125 Patterson Street Neurology Suite 6th Floor New Brunswick, NJ 08901-1977	13
Guttman, Dr. Mark 377 Church St., Suite 407 Markham, Ontario L6B 1A1 Canada	22
Hubble, Jean, M.D. Assistant Professor Department of Neurology Kansas University Medical Center 39th and Rainbow Blvd. Kansas City, KS 66103	16
Jankovic, Joseph, M.D. Professor of Neurology Baylor College of Medicine Dept. of Neurology 6550 Fannin Street, Suite 1801 Houston, TX 77030	14
Karp, Jeffery, M.D. Tampa Bay Medical Research 3253 McMullen Booth Road, Suite 200 Clearwater, FL 34621-2010	14
King, Dr. David B 5523 Spring Garden Road, Suite 208 Halifax, Nova Scotia Canada B3J 3T1	20
Lieberman, Abraham, M.D. Chief, Motor Disorders St. Joseph Hospital Barrow Neurological Institute 222 W. Thomas Road, Suite 401 Phoenix, AZ 85013	20
Montgomery, Erwin, M.D. Associate Prof., Dept. of Neurology University Physicians Neurology Clinic 1745 North Campbell Avenue Tucson, AZ 85719	10

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Olanow, C Warren, M.D. (1/19/93-6/12/94) Hauser, Robert A, M.D. (6/13/94-present) Assistant Professor of Neurology Department of Neurology Harbour Side Medical Tower 4 Columbia Drive, Suite 410 Tampa, FL 33606	12
Paulson, George, M.D. Chairman, Department of Neurology 452 Means Hall Ohio State Univ. School of Medicine 1655 Upham Drive Columbus, OH 43210	7
Perlmutter, Joel S, M.D. Assoc. Professor of Neurology Washington Univ. School of Medicine Dept. of Neurology 660 South Euclid P. O. Box 8111 St. Louis, MO 63110	6
Pfeiffer, Ronald F, M.D. (3/17/93-6/19/94) Bertoni, John, M.D.,Ph.D. (6/20/94-present) University of Nebraska Medical Center Division of Neurology 42nd Street and Dewey Avenue Omaha, NE 68105	12
Pincus, Jonathan, M.D. Chairman, Dept. of Neurology Georgetown University Hospital 3800 Reservoir Road, N.W. Suite 1 Bles Washington, D.C. 20007	10

M/2730/0010	
Name and Address of Investigator	Number of Patients Randomized at Site
Reich, Stephen G, M.D. Asst. Professor of Neurology Johns Hopkins University School of Medicine Outpatient Center 601 N. Caroline St., Suite 5070 Baltimore, MD 21282	5
Richter, Ralph, M.D. Professor of Neurology St. John's Doctors' Building 1705 E. 19 Street, Suite 406 Tulsa, OK 74104	20
Stoessl, Dr. John Dept. of Clinical Neurological Sciences University Hospital 339 Windermere Road London, Ontario N6A 5A5	14
Tetrud, James, M.D. Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089	18
Waters, Cheryl H, M.D., FRCP(C), FACP Assistant Professor of Neurology Chief, Division of Movement Disorders USC Movement Disorder Clinic Department of Neurology 1510 San Pablo St., Suite 615 Los Angeles, CA 90033	16
Weiner, William, M.D. 1501 N.W. 9th Avenue Parkinson Building Department of Neurology Miami, FL 33136	15

Studies 19 and 22

Title: A double-blind, placebo-controlled, randomized, multi-center study to asses the effects, safety, and tolerance of Pramipexole with concomitant treatment of levodopa (and decarboxylase inhibitor) in advanced Parkinson's disease.

Investigators:

Center	Location	Investigator(s)
19		
2	Austria	Schnaberth Pinter
7	Germany	Conrad
4	Germany	Gehlen
6	Germany	Glab
10	Germany	Kolmel
9	Germany	Oertel
5	Germany	Poewe
22		
1	Denmark	Boas
2	Denmark	Boesen
3	Denmark	Boisen
4	Denmark	Dupont
5	Denmark	Hansen
6	Denmark	Sorensen / Mogensen
7	Denmark	Jensen / Magnussen
8	Denmark	Mikkelsen
9	Denmark	Worm-Petersen

Objectives: The primary objective to assess the effect of Pramipexole (up to 5 mg) on Parkinsonian symptoms versus placebo in patients with advanced Parkinson's disease while on concomitant treatment with levodopa (and decarboxylase inhibitor). Effect is defined as a significant change in the total score of the Unified Parkinson's Disease Rating Scale (UPDRS).

The secondary objective is to asses the safety and tolerance of Pramipexole in variable dose combinations with levodopa (and decarboxylase inhibitor).

Study Design: Multi-center, randomized, prospective, ascending dose, double-blind, placebo controlled study.

Treatments: Ascending dose in weeks one through seven followed by a 4 week maintenance period and a one week taper to discontinue. The maximum dose achieved will be the maximum dose without the patient suffering from intolerable side effects (maximum of 5.0 mg per day in divided doses i.e. 1.25 mg QID).

Treatment(s)	Pramipexole or Placebo	
Week	**Dosage**	**Total Daily Dose**
1	2 x 0.1 mg	0.2 mg
2	4 x 0.1 mg	0.4 mg
3	4 x 0.25 mg	1.0 mg
4	4 x 0.5 mg	2.0 mg
5	4 x 0.75 mg	3.0 mg
6	4 x 1.0 mg	4.0 mg
7	4 x 1.25 mg	5.0 mg

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Please see Table 1 and 2 for the Time and Events for studies 19 and 22, respectively.

Inclusion Criteria:

1. Men; women of non-child bearing potential;
2. Outpatients and Inpatients
3. Age: years (Age: years in study 22).
4. Patients with advanced idiopathic Parkinson's disease (classification according to ICD 9: 332.0) corresponding to stages II-IV according to the classification of Hoehn and Yahr.
5. Patients in whom the individual optimal dosage of levodopa (and decarboxylase inhibitor) causes disturbances such as akinesia, dyskinesia, dystonias, fluctuations.
6. Written informed consent.

Patients were to be maintained on their individual dose of L-dopa (and DCI).
If anticholinergics, amantadine, L-deprenyl, or tricyclic / tetracyclic antidepressant medications were used they should be maintained at a stable dose throughout the trial.

Exclusion Criteria:

1. Symptomatic forms of Parkinson syndrome (e.g. drug induced parkisonism, post-encephalitic parkisonism, Shy-Drager syndrome, Steele-Richardson-Olszewski-Syndrome).
2. Severe dementia
3. epilepsy
4. previous neurological operations

5. severe physical diseases
6. AV block of 2nd or 3rd degree, sick-sinus syndrome, congestive heart failure, myocardial infarction within 6 months before the start of the study.
7. Blood pressure above 180/100 mmHg (patients with a blood pressure below 180/100 mm Hg under concomitant treatment with saluretics, beta-blockers, may be included)
8. Hypotension with systolic blood pressure below 100 mg Hg.
9. Liver disease (SGPT > 82 U/l)
10. Kidney disease (creatinine > 2.5 mg / 100 ml
11. Uncontrolled metabolic diseases
12. Concomitant treatment with bromocriptine, lisuride, other dopamine agonist, apomorphine, MAO-A inhibitors, neuroleptics, alpha-methyldopa, reserpine, clonidine, guanabenz, calcium antagonists
13. Women of child bearing potential (contraceptives are not allowed).

In addition to the above exclusion criteria, in study 22, patients who did not respond to dopamine agonists in the past were excluded from the study. Patients with a history of orthostatic hypotension were excluded.

Study Population:
Please see Table 3.

Outcome Measure: The primary efficacy measure was the change in UPDRS total score (not additionally defined in the protocol) from baseline to the final maintenance period. The total UPDRS score was calculated as the sum of the subscores for I - IV (I - mentation, behavior and mood, II - activities of daily living during "on " and "off" periods, III - motor examination during the "on" periods, and IV - complications of therapy).

Efficacy:

Study 19: An ITT-analysis performed with changes in the UPDRS total score from baseline (visit 2) to the end of the maintenance period (visit 11, week 11) showed a change of 20.1 points (SD=16.0) in the pramipexole treated group vs. A change of 5.9 points (SD=12.8) for the placebo group. The P-value of the Wilcoxon test was 0.0002. In this study the UPDRS sub-score I was not significantly influenced by pramipexole. Please see Table 4.

Study 22: An ITT-analysis performed with changes in the UPDRS total score from baseline (visit 2) to the end of the maintenance period (visit 9, week 11) showed a change of 16.9 points (SD=14.9) in the pramipexole treated group vs. A change of 9.0 points (SD=16.1) for the placebo group. The P-value of the Wilcoxon test was 0.0184. In this study the UPDRS sub-score IV (complications of therapy) was not significantly influenced by pramipexole. Please see Table 4.

In calculating the UPDRS scores, the method of LOCF was utilized. In cases where "on" or "off" scores were to be used and an "off" score was missing, the "on" was utilized. In 19, the number of scores missing was comparable in the two groups, as were the number of values missing from the most important visits (baseline and final maintenance visits). In contrast, the percent of missing values was substantially higher in the active drug group vs. the placebo group for study 22). This

difference was most notable for the final maintenance visit. Please see Table 5.

It is interesting to note than at one center (6, Sorensen and Mogensen) in study 22, the patients receiving Pramipexole, showed less improvement than the placebo group. This is the only center where this trend was noted.

Concomitant L-dopa Treatment: In study 19, treatment did not result in changes in the concomitant L-dopa (DCI). In contrast in study 22, the change (reduction in dose) from baseline to the end of the maintenance period was 150.7 mg/d in the pramipexole group compared to a change of 10.6 mg/d in the placebo group. Please see Table 6.

Safety: Please see the separate safety review for a more detailed evaluation. No deaths were reported in either study. In study 19, one patient in the Pramipexole group experienced angina pectoris which resulted in hospitalization. One patient in the placebo group experienced worsening of his Parkinsonian symptoms and developed papillary bladder carcinoma. He recovered from the former during the study and the latter during the follow-up. Eight patients withdrew from the study due to adverse events. Three from the active group and five from the placebo group. In former, one patient withdrew due to sedation/tiredness, one due to decreased blood pressure and confusion, and one due sleepiness and myoclonia. In study 22, There were three withdrawals due to adverse events, 1 form the Pramipexole group for orthostatic hypotension and 2 from the placebo group, 1 for angina pectoris and one for severe repetitive tachycardia. Please see Table 7.

Summary:

1. Patient Selection: Study 22 excludes patients who have not responded to dopamine agonists.
2. Demographics: In study 19 there is a disparity between the number of patients in the active vs. placebo groups. In addition, in this study, there is a higher percentage of male subjects in the placebo group. There is an imbalance in the treatment groups. The age, weight, duration of PD, and total UPDRS scores are comparable between the active and placebo groups in both studies. There is a greater percentage of Hoehn & Yahr stage IV patients in the placebo group vs. active group in both studies. This would suggest that the active groups had patients with less severe PD, and might be expected to do better than the placebo groups. Further suggestion of this is seen in the stratification based on L-dopa and other anti-Parkinson's disease medications, where the placebo group has a larger percent of patient's in the > 600 mg of L-Dopa groups. In study, 22, the stratification is based only on the amount of L-Dopa and does not include other anti-Parkinson's disease medications.
3. Exclusion Criteria: In study 22, patients who did not respond to dopamine agonists were excluded from the study. This exclusion has the potential to bias patient selection, in that patients are selected, who have previously demonstrated that they will benefit from a dopamine agonist. Another exclusion criteria included in study 22 was that of excluding patients with orthostatic hypotension. This is a frequent complication of Parkinson's disease, as well as a potential side effect several medications used to treat PD. These exclusion should be considered in preparation of the product labeling.
4. Efficacy: The primary endpoint analysis based on the protocols is the total UPDRS score. In both

studies, in either evaluable or ITT analysis, there is significant improvement in the UPDRS Total score. Improvement is seen in subparts II (activity of daily living), III (motor examination), and IV (complications). Patients receiving active drug had better scores in the Global Clinical Assessment and percent of off time during waking hours. There was no treatment effect with respect to the dyskinesia scale.

5. The mean daily dose of pramipexole was 3.59 and 4.59 in study 19 and 22, respectively.

Conclusion: Based on the primary outcome proposed in the protocols, change of the UPDRS Total score, the sponsor has demonstrated efficacy of the active drug, Pramipexole, in studies 19 and 22.

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