

**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 not in the study report.
2. Plasma levels of concomitant deprenyl and anticholinergics were not measured during the conduct of this trial.

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**E. Conclusions**

A linear dose-response relationship was not demonstrated in this study. All doses performed equally.

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TR No.: 7217-95-037

**Upjohn** STEP-UP  
EUROQOL QUESTIONNAIRE (Part 1 of 2)

93-0286-28 3-84		<b>DO NOT WRITE IN SHADED AREAS</b>			
PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.	
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE	DATE OF THIS REPORT	MO.	DAY	YR.
					SITE NO.

**INSTRUCTIONS:** Please check the answer that best describes your (the patient's) health state today.

- |  |   |
|--|---|
| <p><b>1. Mobility:</b></p> <p><input type="checkbox"/><sub>0</sub> I have no problems walking about</p> <p><input type="checkbox"/><sub>1</sub> I have some problems walking about</p> <p><input type="checkbox"/><sub>2</sub> I am confined to bed</p> <p><b>2. Self-care:</b></p> <p><input type="checkbox"/><sub>0</sub> I have no problems with self-care</p> <p><input type="checkbox"/><sub>1</sub> I have some problems washing or dressing myself</p> <p><input type="checkbox"/><sub>2</sub> I am unable to wash or dress myself</p> <p><b>3. Usual Activities:</b></p> <p><input type="checkbox"/><sub>0</sub> I have no problems with performing my usual activities (e.g., work, study, housework, family or leisure activities)</p> <p><input type="checkbox"/><sub>1</sub> I have some problems with performing my usual activities.</p> <p><input type="checkbox"/><sub>2</sub> I am unable to perform my usual activities.</p> | <p><b>4. Pain/Discomfort:</b></p> <p><input type="checkbox"/><sub>0</sub> I have no pain or discomfort</p> <p><input type="checkbox"/><sub>1</sub> I have moderate pain or discomfort</p> <p><input type="checkbox"/><sub>2</sub> I have extreme pain or discomfort</p> <p><b>5. Anxiety/Depression:</b></p> <p><input type="checkbox"/><sub>0</sub> I am not anxious or depressed</p> <p><input type="checkbox"/><sub>1</sub> I am moderately anxious or depressed</p> <p><input type="checkbox"/><sub>2</sub> I am extremely anxious or depressed</p> |
|--|---|
- APPEARS THIS WAY  
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- 6. Compared with my general level of health over the past 12 months, my health state today is:**
- <sub>1</sub> Better
- <sub>2</sub> About the same
- <sub>3</sub> Worse

COMMENTS:

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TR No.: 7217-95-037

**Upjohn** STEP-UP  
EUROQOL QUESTIONNAIRE (Part 2 of 2)

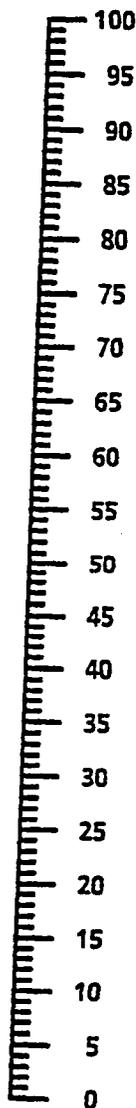
91-0264-29 3-94

PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100, and the worst state you can imagine is marked by 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health state is.

Best imaginable health state



Your Own Health State Today

Worst imaginable health state

SCALE SCORE:

INITIALS or SIGNATURE:

SHEET NO.

25

TR No.: 7217-95-037



STEP-UP

**DAILY ACTIVITIES - FUNCTIONAL STATUS QUESTIONNAIRE<sup>®</sup> - Page 1 of 6**

93-0286-02 1-84

To be answered by the patient

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PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE	DATE OF THIS EVALUATION	MO. / DAY / YR.	SITE NO.

This group of questions refers to many types of physical and social activities. We would like to know how difficult it was for you to do each of these activities, on the average, during the past month. By difficult, we mean how hard it was or how much physical effort it took to do the activity because of your health.

Circle the number:

- 4 if you usually had no difficulty doing it;
- 3 if you usually had some difficulty doing it;
- 2 if you usually had much difficulty doing it;
- 1 if you usually did not do the activity because of your health; or
- 0 if you usually did not do the activity for other reasons.

DURING THE PAST MONTH, HOW MUCH PHYSICAL DIFFICULTY DID YOU HAVE . . .	USUALLY DID WITH NO DIFFICULTY	USUALLY DID WITH SOME DIFFICULTY	USUALLY DID WITH MUCH DIFFICULTY	USUALLY DID NOT DO BECAUSE OF HEALTH	USUALLY DID NOT DO FOR OTHER REASONS
1. Taking care of yourself, that is, eating, dressing, or bathing?	4	3	2	1	0
2. Moving in and out of a bed or chair?	4	3	2	1	0
3. Walking <u>several</u> blocks (a few hundred meters or yards)?	4	3	2	1	0
4. Walking <u>one</u> block or climbing <u>one</u> flight of stairs? (30-40 meters or yards)	4	3	2	1	0
5. Walking indoors, such as around your home?	4	3	2	1	0
6. Doing work around the house such as cleaning, light gardening, home maintenance?	4	3	2	1	0
7. Doing errands, such as grocery shopping?	4	3	2	1	0
8. Driving a car or using public transportation?	4	3	2	1	0
9. Visiting with relatives or friends?	4	3	2	1	0
10. Participating in community activities, such as religious services, social activities, or volunteer work?	4	3	2	1	0

Continued . . .

INITIALS or SIGNATURE:	SHEET NO.	27
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TR No.: 7217-95-037



STEP-UP  
DAILY ACTIVITIES - FUNCTIONAL STATUS QUESTIONNAIRE<sup>®</sup> - Page 2 of 6  
Answered by the Patient

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11-0286-31 1/94

PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.

DURING THE PAST MONTH, HOW MUCH PHYSICAL DIFFICULTY DID YOU HAVE . . .	USUALLY DID WITH NO DIFFICULTY	USUALLY DID WITH SOME DIFFICULTY	USUALLY DID WITH MUCH DIFFICULTY	USUALLY DID NOT DO BECAUSE OF HEALTH	USUALLY DID NOT DO FOR OTHER REASONS
11. Taking care of other people such as family members?	4	3	2	1	0
12. Doing vigorous activities such as running, lifting heavy objects or participating in strenuous sports?	4	3	2	1	0

13. During the past month, how many days did illness or injury keep you in bed all or most of the day? (If none, write "0")  
\_\_\_\_\_ DAYS IN BED during the past month

14. During the past month, how many days did you cut down on the things you usually did for one-half day or more because of your own illness or injury? (Do not count the day(s) spent in bed)  
\_\_\_\_\_ DAYS during the past month

15. Are you unable to do certain kinds or amounts of work, housework, or school or university work because of your health?  
(Circle one)  
YES, for less than 3 months ..... 1  
YES, for 3 or more months ..... 2  
NO, my health was not limited this way ..... 0

16. Does your health keep you from working at a job, doing work around the house, or going to school or university?  
(Circle one)  
YES, for less than 3 months ..... 1  
YES, for 3 or more months ..... 2  
NO, my health was not limited this way ..... 0

17. How do you feel about your own health?  
(Circle one)  
VERY SATISFIED ..... 5  
SATISFIED ..... 4  
NOT SURE ..... 3  
DISSATISFIED ..... 2  
VERY DISSATISFIED ..... 1

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INITIALS or SIGNATURE:	SHEET NO.	28
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TR No.: 7217-95-037

**Upjohn**

STEP-UP

**WELL BEING - FUNCTIONAL STATUS QUESTIONNAIRE<sup>®</sup> - Page 3 of 6**

91-0286-24 3-94

Answered by the Patient

**DO NOT WRITE IN SHADED AREAS**

PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.

These next questions ask about how you feel and how things have been with you during the past month. For each question, please circle the number for the one answer that comes closest to the way you have been feeling.

DURING THE PAST MONTH HOW MUCH OF THE TIME:	ALL OF THE TIME	MOST OF THE TIME	A GOOD BIT OF THE TIME	SOME OF THE TIME	A LITTLE OF THE TIME	NONE OF THE TIME
18. Have you been a very nervous person?	1	2	3	4	5	6
19. Have you felt calm and peaceful?	1	2	3	4	5	6
20. Have you felt down-hearted and blue?	1	2	3	4	5	6
21. Were you a happy person?	1	2	3	4	5	6
22. Did you feel so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
23. Did you isolate yourself from people around you?	1	2	3	4	5	6
24. Were you affectionate toward others?	1	2	3	4	5	6
25. Did you act irritable toward those around you?	1	2	3	4	5	6
26. Did you make unreasonable demands on your family and friends?	1	2	3	4	5	6
27. Did you get along well with other people?	1	2	3	4	5	6

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SHEET NO.

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TR No.: 7217-95-037



**STEP-UP  
SOCIAL ACTIVITIES - FUNCTIONAL STATUS QUESTIONNAIRE<sup>®</sup> - Page 4 of 6**  
*Answered by the Patient*

11-0286-15 3-94

**DO NOT WRITE IN SHADED AREAS**

PRINCIPAL MONITOR G. R. PETERS, M.D.		PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.	

28. About how many close friends do you have - people you feel at ease with and can talk with about what is on your mind? (You may include relatives.)  
 (Enter number on line:)

\_\_\_\_\_ CLOSE FRIENDS AND RELATIVES

29. During the past month, about how often did you get together with friends or relatives, like going out together, visiting in each other's homes, or talking on the telephone?

- |                                     |              |   |
|-------------------------------------|--------------|---|
| EVERY DAY .....                     | (Circle one) | 6 |
| SEVERAL TIMES A WEEK .....          |              | 5 |
| ABOUT ONCE A WEEK .....             |              | 4 |
| 2 OR 3 TIMES DURING THE MONTH ..... |              | 3 |
| ABOUT ONCE A MONTH .....            |              | 2 |
| NOT AT ALL .....                    |              | 1 |

30. During the past month, how satisfied were you with your sexual relationships?

- |   |              |   |
|---|--------------|---|
| VERY SATISFIED .....                        | (Circle one) | 5 |
| SATISFIED .....                             |              | 4 |
| NOT SURE .....                              |              | 3 |
| DISSATISFIED .....                          |              | 2 |
| VERY DISSATISFIED .....                     |              | 1 |
| DID NOT HAVE ANY SEXUAL RELATIONSHIPS ..... |              | 0 |

INITIALS or SIGNATURE:	<i>Continued ...</i>	
	SHEET NO.	30

TR No.: 7217-95-037



**STEP-UP  
EMPLOYMENT - FUNCTIONAL STATUS QUESTIONNAIRE<sup>®</sup> - Page 5 of 6**  
Answered by the Patient

**DO NOT WRITE IN SHADED AREAS**

PRINCIPAL MONITOR <b>G. R. PETERS, M.D.</b>		PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. <b>M / 2730 / 0004</b>	STUDY PERIOD <b>BASELINE</b>			SITE NO.	

The next question concerns your present working situation other than managing your home.

31. Which of the following statements best describes your work situation during the past month?

- WORKING FULL-TIME .....
- WORKING PART-TIME .....
- UNEMPLOYED, LOOKING FOR WORK .....
- UNEMPLOYED BECAUSE OF MY HEALTH .....
- RETIRED BECAUSE OF MY HEALTH .....
- RETIRED FOR SOME OTHER REASON .....
- OTHER .....

(Circle one)

1	}	Go to #32
2		
3	}	Go to Next Page
4		
5		
6		
7		

DURING THE PAST MONTH, HOW MUCH OF THE TIME DID YOU:	ALL OF THE TIME	MOST OF THE TIME	SOME OF THE TIME	NONE OF THE TIME
32. Do as much work as others in similar jobs?	1	2	3	4
33. Work for short periods of time or take frequent rests because of your health?	1	2	3	4
34. Work your regular number of hours?	1	2	3	4
35. Do your job as carefully and accurately as others with similar jobs?	1	2	3	4
36. Work at your usual job, but with some changes because of your health (for example, use special equipment, trade tasks with other workers)?	1	2	3	4
37. Fear losing your job because of your health?	1	2	3	4

INITIALS or SIGNATURE:	SHEET NO.	Continued ... <b>31</b>
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TR No.: 7217-95-037



**STEP-UP  
EMPLOYMENT - SUPPLEMENTAL - Page 6 of 6**  
Answered by the Patient

93-07286-37 3-94

DO NOT WRITE IN SHADED AREAS

PRINCIPAL MONITOR G. R. PETERS, M.D.	PRINCIPAL INVESTIGATOR	INVESTIGATOR'S NO.	SUBJECT'S INITIALS	SUBJECT NO.
PROTOCOL NO. M / 2730 / 0004	STUDY PERIOD BASELINE			SITE NO.

**INSTRUCTIONS:** If, based on question 31 on the previous page, you are:  
 • working full or part time, go to part A below.  
 • retired for any reason or unemployed for health reasons, go to Part B below (skip part A).  
 Otherwise, skip parts A, B, and C. You have completed this questionnaire.

**PART A.** For those working full or part-time according to question 31:

- A1. How many hours do you normally work per week? \_\_\_ hours
- A2. In the last month, approximately how much work time have you missed due to problems resulting from your Parkinson's Disease?  
 \_\_\_ Days (enter 0 if you did not miss any work time)

GO TO PART C BELOW (skip part B).

**PART B.** For those retired for any reason or unemployed for health reasons based on question 31:

- B1. Are you currently unemployed, or did you retire early, because of your Parkinson's Disease:  
 1 Yes (go to next question)  
 0 No (go to Part C below)
- B2. How long have you been retired or unemployed solely because of your Parkinson's Disease? (Do not count time since your normal retirement age):  
 \_\_\_ years, \_\_\_ months

GO TO PART C BELOW.

**PART C.**

Please check the category below which best describes the kind of work you do (or did) on your current (or most recent) job:

- 1 Professional, technical or related
- 2 Administrative or managerial
- 3 Clerical or related
- 4 Sales
- 5 Service (including all food and lodging services)
- 6 Agriculture, animal husbandry, forestry, fishing
- 7 Production or related work, transport equipment operators or laborers
- 8 Armed forces
- 9 None of the above

(If you have trouble picking the best category please ask the study nurse or doctor for assistance. A detailed list of occupations by category is provided in the operations manual.)

INITIALS or SIGNATURE:	SHEET NO.	32
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M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Brin, Mitchell, M.D. Bressman, Susan, M.D. Columbia University 710 W. 168th, Rm. 309 New York, NY 10032	15
Gauthier, Serge, M.D. McGill Ctr. for Studies in Aging St. Mary's Hospsital 3830 Lacombe Avenue Montreal, Quebec H3T 1M5 Canada	6
Grimes, J. David, M.D. Ottawa Civic Hospital Ottawa, Ontario K1Y 4E9 Canada	15
Harrison, Madaline B., M.D. Dept. of Neurology, Box 394 Univ. of Virginia Health Sciences Ctr. Charlottesville, VA 22908	10
Hauser, Robert, M.D. (6/13/94 - present) Olanow, C. Warren, M.D. (1/19/93 - 6/12/94) University of South Florida 4 Columbia Dr., Suite 410 Tampa, FL 33606	15
Hubble, Jean, M.D. Univ. of Kansas Medical Center Department of Neurology 3901 Rainbow Blvd. Kansas City, KS 66160-7314	10
Hurtig, Howard I, M.D. The Graduate Hospital University of Pennsylvania Department of Neurology 1 Graduate Plaza Philadelphia, PA 19146	18

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Kurlan, Roger, M.D. University of Rochester Department of Neurology 601 Elmwood Avenue, Box 673 Rochester, NY 14642	15
Lew, Mark F, M.D. Univ. of Southern California Department of Neurology USC School of Medicine 1510 San Pablo, Suite 615 Los Angeles, CA 90033	20
Marek, Kenneth I, M.D. Yale Univ. School of Medicine Department of Neurology 333 Cedar Street New Haven, CT 06510	11
Perlmutter, Joel, M.D. Washington Univ. School of Medicine Neurology, Campus Box 8225 510 S. Kings Highway St. Louis, MO 63110	7
Rajput, Ali H, M.D. University of Saskatchewan Clinical Neurology, Rm 1663 Royal University Hospital Saskatoon, SK S7N 0X0 Canada	10
Rao, Jayaraman, M.D. LSU Medical Center 1542 Tulane Avenue New Orleans, LA 70112	15
Rodnitzky, Robert, M.D. University of Iowa Department of Neurology University Hospitals Iowa City, IA 52242	12
Sethi, Kapil D, M.D. Medical College of Georgia B1W-340 Dept. of Neurology 1120 15th Street Augusta, GA 30912	15

M/2730/0004	
Name and Address of Investigator	Number of Patients Randomized at Site
Shannon, Kathleen M, M.D. Rush-Presbyterian/St. Luke's Medical Center Dept. of Neurological Sciences 1725 W. Harrison, Suite 1106 Chicago, IL 60612	14
Suchowersky, Oksana, M.D. Univ. of Calgary/Foothills Hospital 3350 Hospital Drive, NW Calgary, Alberta T2N 4N1 Canada	10
Tanner, Caroline M, M.D. The Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089	14
Trosch, Richard, M.D. Sinai Hospital of Detroit Clinical Neuroscience Program Blumberg Professional Offices 14800 W. McNichols Rd., Suite 100 Detroit, MI 48235	19
Weiner, William, M.D. Univ. of Miami School of Medicine Department of Neurology National Parkinson Foundation 1501 NW 9th Avenue Miami, FL 33136	13

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## Study 17

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 early-onset PD patients who had not received more than 3 months of L-dopa in the past. Concomitant anticholinergics were allowed. Concomitant amantadine was prohibited. All patients were on deprenyl.

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 and III of the UPDRS. The primary outcome was mean change from baseline on Parts II and III of the UPDRS at the end of maintenance.

### **Results:**

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Fifty-six patients were randomized; only 55 ever received a first dose, so that the ITT population includes 55 patients. The sponsor has provided an analysis of an evaluable data set, which excludes 2 patients that the sponsor believes were shown after randomization to not have idiopathic PD. One of the 2 pts was replaced, but the second patient was reclassified after the trial was over and, thus, could not be replaced.

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.]

Adjusted Change From Baseline, UPDRS II

Pramipexole	5.19 (n=28)	
Placebo	2.16 (n=24)	p=0.002

Adjusted Change From Baseline, UPDRS III

Pramipexole	11.97 (n=27)	
Placebo	8.31 (n=24)	p=0.10

There were no deaths or serious AEs. There was only one discontinuation for AE, a placebo patient with worsening of PD. Ten patients (1 placebo; 9 pramipexole) had dose-limiting toxicity from AEs, to include hallucinations, violent dreams, insomnia, and drowsiness.

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**Conclusions:**

Hallucinations resulted in dose-limiting toxicity in 3 pramipexole patients. Note that the primary outcome encompassed Parts II and III of the UPDRS, so that a favorable score on those subscales could be recorded in the face of serious AEs that required dose adjustments.

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

While more patients may have improved on the ADL scale while on pramipexole as opposed to placebo, some pramipexole patients had serious AEs (hallucinations) requiring dose adjustments. Given the brief maintenance period, it is unknown how long the risk-benefit ratio would have continued in favor of pramipexole.

It is reassuring that the estimates of change from baseline on the ADL scale here are so similar to those seen in Study 21 (a study very comparable in design to Study 17). The difference on the ADL scale is statistically significant here, but not in Study 21.

On the other hand, the estimates of change from baseline on the Motor Exam scale here are different from those in Study 21. The directionality favors pramipexole in both studies, but is statistically significant only in Study 21.

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## Study 21

This was designed to be a double-blind, placebo-controlled, parallel-group study of a maximal-tolerated-dose of pramipexole vs. placebo. By design 52 patients were required to complete the maintenance dose schedule; in order to achieve this, the protocol called for 72 patients to be randomized.

Patients were early-onset PD patients who had not received more than one week of L-dopa in the past. Concomitant anticholinergics and deprenyl were allowed. Concomitant amantadine was prohibited. Domperidone was allowed.

There was a 9-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 1 or 2 levels. Following dose-escalation, there was a 2 week maintenance period and then a 1 week dose reduction period.

Assessment included Parts II and III of the UPDRS. The primary outcome was mean change from baseline on Part III of the UPDRS at the end of maintenance.

### Results:

Only 24 patients were recruited out of the planned 72 before the sponsor stopped the study. The sponsor has provided an analysis of an **explanatory data set**, which excludes a pramipexole patient with a prior history of hallucinations and a placebo patient previously treated for 5 months with L-dopa. The sponsor maintains that these patients did not meet the inclusion/exclusion criteria.

The results for this explanatory data set are shown below:

	Change From Baseline	
Pramipexole	7.2 (n=10)	
Placebo	1.6 (n=12)	p=0.02

The sponsor also examined the results for Part II of the UPDRS (ADL). There was a trend toward improvement following treatment with

pramipexole, but no statistically significant difference. The mean change from baseline for pramipexole was 5 points, while the mean change from baseline for placebo was 2 points.

The sponsor maintains that an improvement of 30% on the motor exam is significant in terms of patient benefit (p 75 of the Technical Report). Using the entire cohort of 24 patients, I categorized patients as 30% improved or not. The results follow:

30% Improved on Motor Exam

Pramipexole	6/11
Placebo	2/13

However, note that 2 placebo patients were withdrawn early (pts 29,76) because of "lack of efficacy" or protocol violation (late recognition that pt had 5 months prior treatment with L-dopa). These represent 2 potential "winners" on placebo who were prematurely taken out of the running. One would assume that "lack of efficacy" would at least have led to further dose escalation, rather than withdrawal. Meanwhile, the 6 pramipexole patients with 30% improvement are balanced by 2 pramipexole patients who discontinued with serious AEs.

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## Conclusions:

The study was stopped early because of low enrollment. The sponsor states that the protocol required weekly visits and that the early PD patients (who were often working) had a hard time making that sort of time commitment.

Two (out of 11) pramipexole patients discontinued because of hallucinations. Note that the primary outcome was the motor exam of the UPDRS, so that a favorable score on that scale could be recorded in the face of serious AEs that required discontinuation.

The maintenance period here was only 2 weeks long, making any extrapolation from these results difficult. (Note also that one pramipexole patient, pt 65, inadvertently skipped the 2-week maintenance phase so that the score at end of dose-escalation was used for outcome assessment.)

While more patients may have improved on the motor exam while on pramipexole as opposed to placebo, 2 pramipexole patients had serious AEs (hallucinations) requiring discontinuation. Given the brief maintenance period, it is unknown how long the risk-benefit ratio would have continued in favor of pramipexole.

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## Study 10

### A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of pramipexole vs. placebo, added on to maintenance L-dopa (with a decarboxylase inhibitor) therapy. The treatment periods were designed to be at least 6 months in duration.

The target population were patients with a less than optimal response to L-dopa, characterized by the presence of motor fluctuations. 300 patients were to be entered, 150 per treatment group. A total of 24 centers in the U.S. and Canada were planned with up to 24 patients per center.

#### Inclusion criteria were:

1. Patients with idiopathic Parkinson's disease, Hoehn and Yahr Scale scores of II-IV during an on period, age 30 years and older. Scores of II-IV encompass patients with bilateral disease with minimal-severe disability and balance problems. A score of V would be given to a bedbound or wheelchair-bound patient. A score of I would be given to a patient with only unilateral disease.
2. Given a stable dose of L-dopa for 30 days prior to randomization, patients had to demonstrate continued motor fluctuations, specifically the so-called "wearing-off" effect, where the duration of effect from a single dose of L-dopa becomes progressively shorter over time.

Page 11 of the protocol added that, if the patient was taking deprenyl, amantadine, or and anticholinergic medication, the dose of that medication should be stable for 30 days prior to randomization.

3. Patients had to be able to keep an accurate daily diary of "on" and "off" periods during waking hours, with the help of caregivers.

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**Exclusion criteria were:**

1. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.
2. Dementia or active psychosis.
3. Second or third degree AV block or sick sinus syndrome; resting heart rate below 50; CHF Class III or IV; MI within 6 months; other clinically significant heart conditions.
4. Occurrence of a seizure within 2 years.
5. Renal or hepatic impairment. Neoplastic disease.
6. Surgery within 6 months which the investigator believes could impact patient's participation.
7. History of stereotactic brain surgery.
8. SBP less than 100 or a symptomatic drop in SBP or 20 or greater upon standing.
9. Neuroleptics within 60 days; alpha-methyl dopa within 60 days; metoclopramide within 60 days; flunarizine, cinnarizine, parenteral ergots, bromocriptine, pergolide, lisuride, MAO inhibitors other than deprenyl, methylphenidate, amphetamine, beta blockers if used to treat tremor, or reserpine within 30 days.
10. Adequate contraception and a negative pregnancy test for all women of childbearing potential.
11. Electroconvulsive therapy within 90 days.

The schedule of time and events is on the next page. Patients were seen for a single **screening visit** within 2 weeks of randomization. At the next visit, if they continued to meet the inclusion/exclusion criteria and if they demonstrated the ability to keep the daily diary, patients were **randomized** to receive the first dose of study medication. An

PRAMIPEXOLE PHASE III TRIAL IN ADVANCED PARKINSON'S DISEASE  
 PROTOCOL SUMMARY - 00879A (Double-Blind, Placebo-Controlled)

Visit Number	Screening	Ascending-Dose Interval <sup>a</sup>										Maintenance-Dose Interval <sup>b</sup>									
		2 <sup>1</sup>	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18 <sup>c</sup>			
Days since the last visit		1-14	5-9	5-9	5-9	5-9	5-9	5-9	10-16	10-16	10-16	10-16	10-16	10-16	10-16	25-35	25-35	25-35			
Dose Level		1	2	3	4	5	6	7	M <sup>1</sup>	M	M	M	M	M	M	M	M	M			
History	X																				
Physical Examination*	X																				
Laboratory Tests*	X				X											X <sup>2</sup>		X <sup>2</sup>			
Chest X-Ray	X																				
12-Lead ECG*	X				X																
Disability Ratings*	X	X	X	X	X	X	X	X	X												
Dispense Daily Patient Records (on/off dates)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Evanescent Daily Patient Records (on/off dates)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events* and Concomitant Meds*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Randomization to Treatment		X																			
Dispense Trial Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Vital Signs*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Medication Compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Motor Examination*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dyskinesia Scales*		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

1. The levodopa/dopa-precursor inhibitor daily dose and timing of dosing must be stable for 30 days prior to Visit 2.
2. Duration of the ascending-dose interval varies depending upon the optimal daily dose of study medication that is achieved. The optimal daily dose is defined as either the maximally tolerated dose of study medication or the dose associated with stable improvement (i.e., lack of further improvement despite up to two additional dose increases). The degree of improvement is based upon the clinical judgement of the investigator without examination of previous scores on various rating scales used in the trial.
3. Maintenance dose (M) is either the maximally tolerated dose or the optimal dose if adverse events do not prevent dose escalation during the ascending-dose interval.
4. Parts I, II, and IV of the UPDRS, Modified Schwab-England Disability Scale, and the timed-walking test (start at Visit 2). Modified Hoehn and Yahr Scale (start at Visit 1).
5. Vital signs (supine and 1 minute standing blood pressure and pulse rate) are taken at Visit 1 in triplicate per protocol, prior to study medication at Visit 2 only and at 2 hours post-dose of study medication at all visits beyond visit 1 as noted above.
6. UPDRS Part III (motor examination) is done two to three hours following a levodopa dose taken either before the clinic visit or at the start of a clinic visit.
7. Parkinson's Dyskinesia Scale done two to three hours following a levodopa dose.
8. Dose-Reduction Interval starts with Visit 18 and ends at Visit 19, the final visit in Part I. See Protocol Summary Part II for specific procedures to be completed for Visit 19.
9. Required for patients who drop from the trial.
10. Blood samples for determination of pramipexole serum concentrations to be obtained.

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**ascending-dose phase** followed and could last as long as 7 weeks. If patients experienced dose-limiting toxicity prior to reaching the maximal dose, they entered the **maintenance phase** at that point (prior to 7 weeks). A patient who moved into the maintenance phase after only 1 or 2 weeks of the ascending-dose phase was considered to have missing data for the additional 5-6 weeks of the ascending-dose phase, resuming entries with visit 9. The maintenance phase was 6 months in duration and was followed by a 1 week **dose reduction phase**.

The ascending dose schedule is on the next page. Study medication was to be taken 1 hour before or 2 hours after meals. There were 7 possible fixed dose regimens, ranging from a total daily dose of . . . . . The dose was to be raised until dose-limiting toxicity was reached, the maximum dose was reached, or there was a lack of further clinical improvement in the judgment of the investigator despite up to two additional increases in the dose of study medication.

The protocol does not have instructions for dose adjustments of study medications if patients developed AEs during the maintenance phase. That is, if a patient developed nausea during the maintenance phase, it is not clear if the dose of study drug could be lowered.

During the maintenance phase, the dose of L-dopa could be adjusted downward if dyskinesias, hallucinations, or psychiatric side effects developed. The dose could subsequently be increased, but not to a level in excess of the original daily dose. Doses of concomitant anticholinergics, deprenyl, and amantadine were to remain constant during the study.

Patient visits occurred every week during the ascending dose phase. Patient visits occurred every 2 weeks for the first 3 months of the maintenance phase and every month for the last 3 months of the maintenance phase.

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## Pramipexole Ascending-Dose Schedule

	<u>Dose Level</u>	<u>Dosage</u>	<u>Total Daily Dose</u>
Week 1	1	3 x 0.125 mg	0.375 mg
Week 2	2	3 x 0.25 mg	0.75 mg
Week 3	3	3 x 0.5 mg	1.50 mg
Week 4	4	3 x 0.75 mg	2.25 mg
Week 5	5	3 x 1.0 mg	3.00 mg
Week 6	6	3 x 1.25 mg	3.75 mg
Week 7	7	3 x 1.5 mg	4.50 mg

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Monthly, during the maintenance phase, the investigator completed the following scales:

1. Parts I, II, and IV of the UPDRS. Part I rates mentation, mood, and behavior. Part II rates ADLs during the past week. Part IV rates complications of therapy, including dyskinesias.
2. Modified Schwab-England Disability Scale
3. Timed Walking Test
4. Modified Hoehn and Yahr Scale

At the same time intervals, the investigator completed the following 2 exams:

1. Part III of the UPDRS (the motor exam). Protocol Amendment #4 clarified that this was to be completed during an "on" period.
2. Parkinson's Dyskinesia Scale

These last 2 exams were to be performed 2-3 hours after the last dose of L-dopa, taken either at home or at the beginning of the clinic visit, and 1-4 hours after the last dose of test drug.

At the same monthly intervals, the investigator evaluated the **daily diaries** for the previous time interval. Patients were instructed to complete the diaries for at least 2 full days prior to their scheduled clinic visits. This was recorded in the CRF as the total waking hours for each day, the number of "off" hours for each day, and the average severity level for the "off" hours in a given day (1-4 scale).

Copies of all scales from the CRF are attached at the end of this Study 10 review. Note that several of the above scales yielded 2 scores, one representing best performance during an "on" period and one representing best performance during an "off" period. This applies to:

1. Part II of the UPDRS
2. Modified Schwab-England Disability Scale
3. Modified Hoehn and Yahr Scale

An operational definition of "on" and "off" was never provided in the protocol. Generally these terms are used to differentiate times when patients are responding well to medicines and periods when they are not

responding well. Off times could occur at predictable times, especially in the time preceding the next dose of medicine. Off times could also occur at unpredictable times, unrelated to time of medicine. The latter unpredictable off times could be brief, referred to as "freezing," or they could be more prolonged. Off time may not represent as low a level of functioning as might be seen in the total absence of medicine, but is generally referenced to a better level of functioning that occurs on the same daily dose of medication.

**Replacement** of patients was allowed by protocol if those patients discontinued the study for any reason other than AEs (to include worsening of underlying Parkinson's Disease) prior to completing half of the maintenance phase. **Protocol Amendment #1** added that patients who dropped out of the study prior to completing the maintenance phase were to return for a final visit at the time their final visit would have occurred.

Note that during the ascending-dose phase, patients assigned to the pramipexole group received both pramipexole and placebo tablets; patients assigned to the placebo group were not exposed to pramipexole.

**Two primary outcome variables** were stated in the protocol: Part II of the UPDRS (ADL) and Part III of the UPDRS (motor exam).

**The analysis plan** stated that "the primary efficacy endpoint for each of these parts of the UPDRS is the change in the score between baseline and maintenance where the maintenance score is the last available score prior to the dose-reduction interval." The primary analysis plan was not clearly specified in the protocol. **Protocol Amendment #4** clarified this situation. It stated that "In order for this study to be declared positive, both primary endpoints must achieve statistical significance." The ITT population was to be the primary analysis population with an LOCF technique employed for missing data.

**The sample size** was computed using results in the DATATOP study and making assumptions about how the early Parkinson's Disease population in DATATOP might differ from the target population in the current study. It was estimated that with 150 patients per treatment group, the study would have 90% power to detect small differences on the order of 2-4 points in change from baseline in Part III of the UPDRS (motor exam).

## B. Subject Disposition and Baseline Comparison

The planned enrollment was 300, with plans to replace patients who did not complete half the maintenance phase for reasons other than AEs. On page 37 of the study report, the sponsor states that enrollment exceeded the planned enrollment because, by the time it became apparent that enough patients would complete the trial, other patients were already enrolled in earlier stages of the trial.

360 patients were randomized: 181 pramipexole and 179 placebo. The investigators and centers (22 U.S. and 4 Canadian) are listed at the end of this Study 10 review.

Protocol Deviations: 3% of patients entered without meeting all inclusion/exclusion criteria. These included systolic blood pressure < 100, concomitant use of bromocriptine, lack of advanced Parkinson's Disease symptoms, abnormal baseline labs, and prior pramipexole use.

4% of patients had their baseline Sinemet dose exceeded during the trial.

4% of patients took excluded meds during the study to include pergolide, bromocriptine, haloperidol, timolol, and metaclopramide.

37/69 patients who withdrew from the study did not return for the follow-up visit at what would have been Visit 18, as outlined in a protocol amendment.

15% of patients had some baseline testing done after the first dose of study medication. The sponsor states that the first dose was placebo for all patients so that the results should not have been affected.

At least 28% of patients had at least one evaluation performed outside the protocol-specified time interval.

Likewise, at select visits, 10% of patients demonstrated medication compliance less than 75% or greater than 125%.

**Baseline Characteristics:** No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics.

	Placebo N=179	Pramipexole N=181
Age	63 (39-89)	63 (31-84)
Sex	116M/63F	119M/62F
Race	96% White	95% White
Parkinson's Duration	9 yrs	9 yrs
Deprenyl Use	53%	56%
Anticholinergic Use	12%	14%
Part II "On" Score	8	7
Part II "Off" Score	17	17
Part III Score	23	23
Hoehn & Yahr "On"	2.3	2.3
Hoehn & Yahr "Off"	2.9	3.0

**Patient Flow:** One patient (placebo) withdrew before receiving drug, so that only 359 patients were treated. Altogether, 9 patients (including the one just mentioned) did not meet the ITT definition, i.e. they did not have at least one efficacy assessment. Therefore, 351 patients are included in the efficacy analysis: 179 pramipexole and 172 placebo.

The following table outlines the withdrawals during the study. In addition to the 68 withdrawals in the table, there was the 1 placebo patient already mentioned who withdrew prior to receiving the first dose. Therefore, there were 69 withdrawals altogether.

Withdrawals (Withdrawals Due to AEs)

	Pramipexole	Placebo
Ascending Dose Phase	12 (9)	22 (16)
Maintenance Phase	18 (15)	16 (14)
TOTAL	30 (24)	38 (30)
	68 (54)	

The timing of the withdrawals had the potential to be important as the protocol allowed for replacement of patients who withdrew prior to visit 15 for reasons other than AEs. However, since only 14 patients withdrew for reasons other than AEs, the latter point took on less importance. As far as I know, there were no replacements during the conduct of the trial. Sponsor's Table 7.3.3:1 on the next page outlines the number of withdrawals by visit for the two treatment groups.

The reasons for withdrawals are shown in the next table.

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Patient Disposition

	Pramipexole	Placebo
Disease Worsening	3	9
Worsening of Pre-existing Disease	0	3
Other AEs	21	18
Protocol Violation	1	0
Lost to Follow-Up	0	2
Withdrew Consent	4	3
Other	1	4

151/181 pramipexole patients completed the trial. 140/179 placebo patients completed the trial.

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Of the 360 patients who were randomized into the trial, 291 patients completed the protocol planned, and 69 patients withdrew. The visits after which these 69 patients withdrew are displayed in TABLE 7.3.3:1.

TABLE 7.3.3:1 Number of Patients Withdrawing from the Trial by Last Visit

Visit	Pramipexole	Cumulative Number (Percentage) of Pramipexole Patients Withdrawing by Visit	Placebo	Cumulative Number (Percentage) of Placebo Patients Withdrawing by Visit
2	0	0 (0%)	3	3 (8%)
3	2	2 (7%)	6	9 (23%)
4	2	4 (13%)	1	10 (26%)
5	1	5 (17%)	5	15 (38%)
6	0	5 (17%)	1	16 (41%)
7	3	8 (27%)	3	19 (49%)
8	1	9 (30%)	3	22 (56%) <sup>1</sup>
9	3	12 (40%)	0	22 (56%)
10	4	16 (53%)	3	25 (64%)
11	6	22 (73%)	5	30 (77%)
12	1	23 (77%)	1	31 (79%)
13	1	24 (80%)	2	33 (85%)
14	1	25 (83%)	1	34 (87%)
15	2	27 (90%)	2	36 (92%)
16	3	30 (100%)	1	37 (95%)
17	0	30 (100%)	1	38 (97%)
18	0	30 (100%)	1	39 (100%)
Total	30		39	

Source Data: Appendix 15.12 LISTINGS 7.1 and 7.2

<sup>1</sup> Patient 1054 discontinued prior to receiving study medication.

Thirty (43%) of the withdrawing patients were from the pramipexole group, while 39 (57%) were from the placebo group. The placebo group had both more withdrawing patients, and also faster withdrawal than the pramipexole group. By Visit 8 over half of the placebo dropouts had occurred, while only 30% of the pramipexole group dropouts had occurred. TABLE 7.3.3:1 also gives the cumulative percentage of dropouts by group for each visit, and it is apparent that dropouts occurred more quickly in the placebo group.

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### C. Efficacy Evaluation

All the analyses in 1-10 below are LOCF analyses, unless specifically described otherwise.

In addition to the 9 patients excluded from all analyses because of lack of any efficacy measurements, some patients had to be excluded from the efficacy analysis for individual efficacy endpoints because of missing data. The sponsor lists all these cases, but they are rare enough that they are not reproduced here. For example, the largest number of patients excluded for a specific endpoint was 12 (3%), which was for the Average Severity of "Off" Time.

On page 62 of the study report, the sponsor addresses the issue of missing data. The sponsor notes the special case where a patient was to be rated for both the on and off periods. This applies to the UPDRS Part II, the Schwab-England Scale, and the Hoehn and Yahr Scale. The sponsor states that "on a few occasions" there was no off score recorded because the patient had no off periods during that particular reporting period. In that situation, the sponsor states that the on score was used to estimate the off score. My review of the data listings suggests otherwise. As shown in the table on the next page, an LOCF approach was used. The number of times that this situation arose is so small that it would not affect the overall results, however.

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**Patients With No Reported OFF Time (by diary) at Visit 18  
and No Recorded OFF Score on UPDRS Part II**

Patient Number	Observed OFF Score (Imputed OFF Score)	Observed ON Score
<b>Placebo Patients</b>		
1035	* (12)	10
1041	* (14)	12
1154	* (13)	7
1294	* (4)	2

<b>Pramipexole Patients</b>		
1072	* (1)	0
1177	* (12)	4
1195	* (0)	2
1200	* (0)	9
1213	* (12)	5
1238	* (12)	1
1264	* (18)	10
1277	* (15)	17
1323	* (1)	0

\* no valued recorded because of lack of "off" periods during that treatment period

[Data taken from Listings 4.5.2, 4.3.2, 4.4.2, and 4.3.1]

## 1. Percentage of On Time, On Time With Dyskinesia, and Off Time:

The percentage of awake time spent in the "off" state was not a primary outcome, but was a secondary outcome. I present this first because it seems to be integral to the whole study. First, the inclusion criteria mandated that patients have on-off phenomenon, especially end-of-dose failure. Second, the two primary outcome variables were defined in terms of on and off time (see below).

Note that, despite the prominent role of the "on-off" phenomenon in this trial, an operational definition is never clearly laid out in the protocol. The instructions for the patient daily diaries define "on" simply as a period of "good motor function." "Off" is defined as "able to move slowly or not at all." In the diaries, off periods were to be graded on a 1-4 scale with the mildest 1 rating defined as "mild slowness, stiffness, or resting tremor." Given this last qualification, one might infer that any emergence of underlying symptoms of Parkinson's Disease in a given patient would meet the definition of "off."

The UPDRS Part II score is an average of an on score and an off score. However, it does not weight the on score and off score with respect to changing amounts of time in the on period and the off period. Theoretically, a patient's on score and off score could both improve, but if more time was spent as off time, the patient would be worse on average, despite a better UPDRS Part II score.

The UPDRS Part III score was collected during an on period. It is called the motor exam portion of the UPDRS, but in fact, an important part of a patient's motor performance, dyskinesia, is not captured in Part III, but is displaced to Part IV.

The protocol defined a positive outcome as a joint outcome, a positive result on Part II and a positive result on Part III. Sponsor's Figures 9.3.1.1.3:1 and 2 on the next page demonstrate quite clearly for both the pramipexole and placebo groups that Parts II and III of the UPDRS are not correlated in Study 10. A patient with improvement on one scale has a fifty-fifty chance of improving on the other. That being the case, a more global assessment of patient function such as percentage off time is informative.

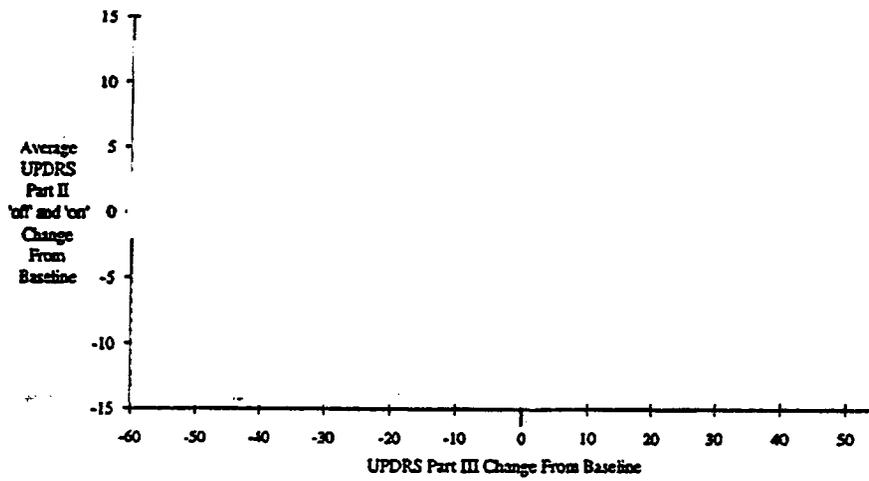


FIGURE 9.3.1.1.3:1 Pramipexole Group Change from Baseline for UPDRS Part II (Averaged) and Part III. Each Point Represents One Patient.

Last Observation Carried Forward Analysis

Source Data: Appendix 15.12.4

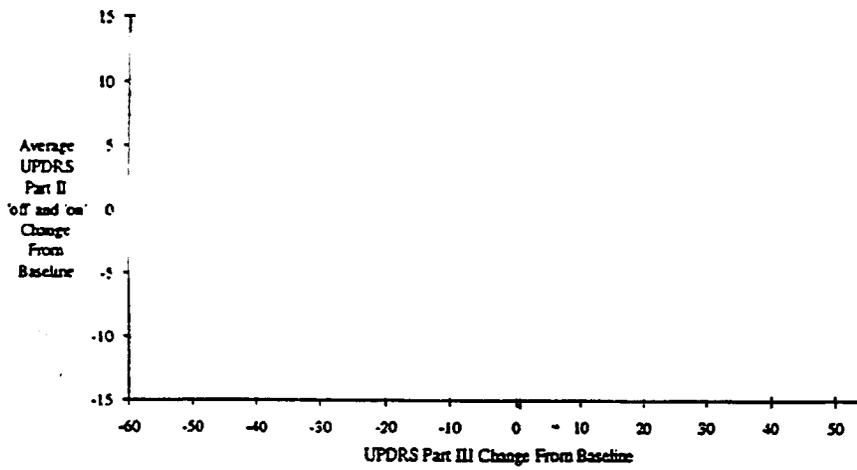


FIGURE 9.3.1.1.3:2 Placebo Group Change from Baseline for UPDRS Part II (Averaged) and Part III. Each Point Represents One Patient.

Last Observation Carried Forward Analysis

Source Data: Appendix 15.12.4

Sponsor's Figure 9.3.1.2.3:1 on the next page shows the average percentage of waking hours spent in an "off" state by visit for the two treatment groups. The information used for this evaluation was collected on the patient daily diary and then summarized by the investigator in the CRF at the time of patient visits. On the patient diary, patients were asked to choose between 4 options: on, off, on with dyskinesia, or asleep. When the investigator summarized this data on the CRF, only the amounts of "off" time and asleep time were transcribed. The sponsor presents the data in terms of percentage of awake time in an "off" state.

The observed case results for the same comparison are not presented by the sponsor.

The sponsor presents an analysis of change from baseline to final results on maintenance. The pramipexole group reduced their percentage of off time by 35% while the placebo group reduced their percentage of off time by 8% ( $p=0.0006$ ).

Note that movement from "off" time could be in the direction of "on" time or "on with dyskinesia" or even "asleep." The sponsor has not provided data on these latter three options separately in the NDA. In fact, data on two of the latter three categories were not transferred from patient diaries to the CRFs. The sponsor addressed this in a September 27 submission.

In that submission the sponsor reports that, at the final maintenance visit, average off hours drop from 6 hrs at baseline to 3.9 hrs in the pramipexole group compared to from 6.2 hrs at baseline to 5.7 hrs in the placebo group. The average awake hrs changed very little throughout the study for both groups.

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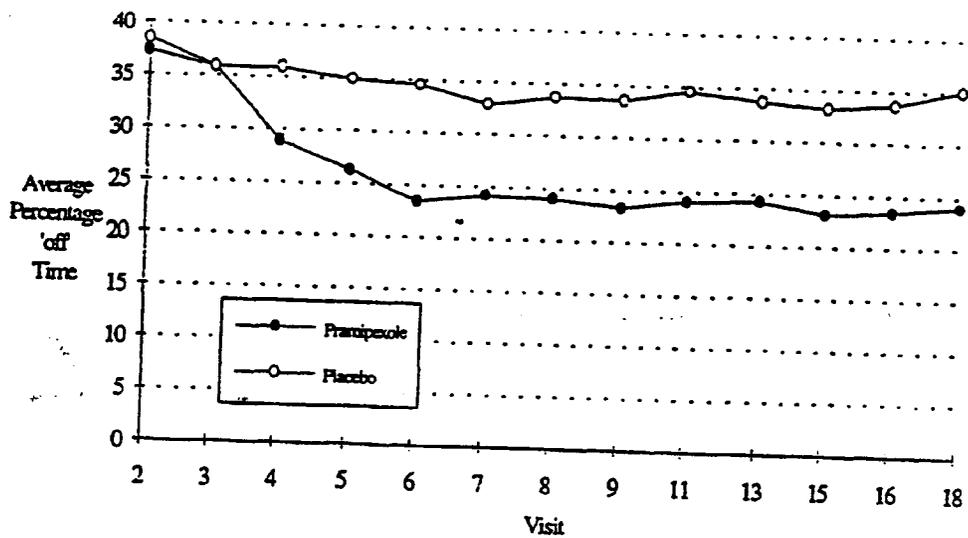


FIGURE 9.3.1.2.3:1 Average Percentage 'off Time by Visit.

Last Observation Carried Forward Analysis

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TABLE 9.3.1.2.3:2 Mean (S.D.) Average Percentage of 'off Period Time Change from Baseline.

Last Observation Carried Forward Analysis

	Baseline	Final Maintenance Visit	Unadjusted Change from Baseline to Final Visit on Maintenance	Adjusted <sup>1</sup> Change from Baseline to Final Visit on Maintenance
Pramipexole n = 173	37.20 (19.91)	24.01 (22.45)	-13.18 (22.15)	-11.70
Placebo n = 172	38.28 (20.35)	35.13 (24.24)	-3.15 (23.20)	-2.82
p-value				0.0005

Source Data: Appendix 15.9.2 STATDOC 4.5.3

<sup>1</sup> Adjusted by center and center-by-treatment interaction (as per protocol).

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But there is an even more confusing issue raised by the data. In the table on the next page is a listing of patients who rated themselves as having no "off" time at visit 18, yet who were given "off" ratings on UPDRS Part II. This is incongruous. How could a patient have a score for a physiologic state that did not occur? The answer is that off periods did occur for these patients, but were not captured in the diary data.

In the September 27 submission, the sponsor reports frequency tables of number of days in the CRF diary at each visit for the two treatment groups. Patients were told to record diaries for at least 2 days prior to the next clinic visit; the CRF provided space to transcribe diary data for up to 10 days. Obviously, this presents a problem when looking at the last 3 months of maintenance, when pts were seen only once monthly. Two days may not capture the true experience of the month.

In fact the instructions for the diaries state, "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." This implies an intent to analyze diary data weekly, an intent that could not be realized because of the study design which collected only snapshots of diary information every 30 days.

Reassuring is the fact that the snapshots were collected every 30 days and show a consistent trend in favor of the pramipexole group.

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**Patients With No Reported OFF Time (by diary) at Visit 18**

Patient Number	Observed OFF Score	Observed ON Score
<b>Placebo Patients</b>		
1168		
1169		
1222		
1311		
1358		

<b>Pramipexole Patients</b>		
1030		
1093		
1156		
1157		
1171		
1228		
1230		
1232		
1234		
1250		
1255		
1295		
1306		
1316		
1321		
1368		
1385		
1413		

Table D1  
Frequency Tables of the Number of Days in the Diary at Each Visit  
M/2730/0010

Visit	MC	Number of Days in the Diary										total N	p-value
		1	2	3	4	5	6	7	8	9	10		
Visit 2 (baseline)	PPX	6	47	29	32	13	18	11	5	3	11	175	0.896
	PBO	2	56	25	32	9	19	13	6	3	13	178	
Visit 3 (week 1)	PPX	0	53	24	27	12	20	28	9	2	3	178	0.829
	PBO	0	50	31	26	14	21	18	5	2	3	170	
Visit 4	PPX	0	50	28	27	7	30	26	4	2	3	177	0.911
	PBO	0	53	32	21	4	24	23	2	2	2	164	
Visit 5	PPX	0	53	17	25	9	20	23	9	3	1	160	0.459
	PBO	0	46	28	21	10	17	25	6	0	2	155	
Visit 6	PPX	0	50	19	22	12	20	18	7	1	2	151	0.643
	PBO	0	48	22	21	10	22	22	2	2	0	149	
Visit 7	PPX	0	44	17	21	8	15	22	0	4	1	132	0.592
	PBO	1	45	19	19	8	19	15	4	3	2	135	
Visit 8	PPX	0	38	11	16	5	13	17	3	2	0	105	0.922
	PBO	2	43	14	19	6	14	17	3	3	2	123	
Visit 9 <sup>ⓐ</sup>	PPX	0	58	20	31	7	21	21	5	1	1	165	0.687
	PBO	0	53	26	23	7	18	24	2	3	0	156	
Visit 10	PPX	0	48	15	30	3	5	6	6	5	42	160	0.620
	PBO	1	46	23	32	0	4	6	4	6	34	156	
Visit 11	PPX	0	46	15	36	8	3	6	4	9	36	163	0.096
	PBO	1	39	26	32	1	2	5	3	2	40	151	
Visit 12	PPX	3	42	17	31	3	4	6	4	4	40	154	0.907
	PBO	3	35	22	32	1	1	5	4	3	39	145	
Visit 13	PPX	0	42	16	32	6	7	10	5	4	32	154	0.084
	PBO	2	39	22	27	2	1	9	0	2	36	140	

ⓐ Maintenance Week 0

# End of Maintenance week 24

APPEARS THIS WAY  
ON ORIGINAL

Table D1  
 Frequency Tables of the Number of Days in the Diary at Each Visit  
 M/2730/0010

Visit	MC	Number of Days in the Diary										total N	p-value
		1	2	3	4	5	6	7	8	9	10		
Visit 14	PPX	2	44	15	33	1	6	8	7	2	35	153	0.552
	PBO	2	39	20	27	1	3	6	1	5	32	136	
Visit 15	PPX	1	45	12	34	3	5	7	4	6	31	148	0.747
	PBO	1	41	21	30	2	4	2	3	50	30	139	
Visit 16	PPX	1	42	15	24	5	4	8	8	4	39	150	0.987
	PBO	1	39	17	28	4	3	8	4	3	35	142	
Visit 17	PPX	2	42	14	24	6	3	7	10	7	32	147	0.884
	PBO	3	40	19	24	2	4	6	6	5	31	140	
Visit 18 #	PPX	2	37	17	24	4	2	3	10	6	40	145	0.902
	PBO	3	42	19	23	3	3	4	6	7	28	138	

@ Maintenance Week 0  
 # End of Maintenance week 24

APPEARS THIS WAY  
 ON ORIGINAL

APPEARS THIS WAY  
 ON ORIGINAL