Study 1

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of pramipexole vs. placebo. Randomization was stratified for concurrent l-deprenyl use. The treatment periods were designed to be at least 6 months in duration.

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 30 patients per center.

Inclusion criteria were:

1. Patients with early, symptomatic, idiopathic Parkinson's disease, Hoehn and Yahr Scale scores of I-III, age 25 years and older. Patients could not be taking L-dopa currently.

Exclusion criteria were:

1. Previous treatment with L-dopa for more than 180 days (6 months) and/or within 60 days of Visit 2.

2. Previous treatment with amantadine within 21 days of Visit 2.

3. Previous treatment with direct-acting dopamine receptor agonists.

4. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.

5. Dementia or active psychosis.

6. 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.

7. Occurrence of a seizure within 2 years.

8. Renal or hepatic impairment. Neoplastic disease.

9. Surgery within 6 months which the investigator believes could impact patient's participation.

10. History of stereotactic brain surgery.

11. SBP less than 100 or a symptomatic drop in SBP of 20 or greater upon standing.

12. Neuroleptics within 60 days; alpha-methyl dopa within 60 days; metoclopramide within 60 days; flunarizine, cinnarizine, parenteral ergots, MAO inhibitors other than deprenyl, methylphenidate, amphetamine, beta blockers if used to treat tremor, or reserpine within 30 days.

13. Adequate contraception and a negative pregnancy test for all women of childbearing potential.

14. Electroconvulsive therapy within 90 days.

Note that the Inclusion/Exclusion criteria do not specifically address the issue of prior or current use of anticholinergic drugs, but the protocol (p11) states that patients may be treated with one concurrent anticholinergic medication at a fixed daily dose.

The schedule of time and events is attached. 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, patients were **randomized** to receive the first dose of study medication. An **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.**

M/2730/0001

PRAMIPEXOLE PHASE III TRIAL IN EARLY PARKINSON'S DISEASE
PROTOCOL SUMMARY - PART I (Double-Blind, Placebo-Controlled)

	S	Ascending-Dose Interval[1]							Maintenance-Dose Interval[2]									
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18[5]
Days since the last visit		1-14	5-9	5-9	5-9	5-9	5-9	5-9	5-9	10-16	10-16	10-16	10-16	10-16	10-16	25-35	26-35	25-35
Dose Level		1	2	3	4	5	6	7	M[3]	M	M	M	M	M	M	M	M	M
History	x																	
Physical Examination*	x																	
Laboratory Tests*	x				x				x				x			x		x
Chest X-ray	x																	
12-Lead ECG*	x				x				x				x			x		x
Disability Ratings[3*]	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 Study Medication		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs[4]	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

1. 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 the tolerated dose of study medication 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.
2. 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.
3. UPDRS Part II (activities of daily living) and Part III (motor examination) start at Visit 2. The motor examination is to be done 2 to 3 hours after study medication is administered except for Visit 2 (done prior to the dose of study medication administered in the clinic). Modified Hoehn and Yahr Scale at Visit 1 only.
4. 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.
5. Dose-reduction interval starts with Visit 18 and ends at Visit 19, the final visit in Part 1. See Protocol Summary Part II for specific procedures to be completed for Visit 19.

* Required for patients who drop from the trial

S = Screening

The ascending dose schedule is attached. 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 _ mg. 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.

The protocol **does state** (p16) that patients receiving anticholinergic medication should not have dose adjustments. Patients on l-deprenyl were allowed to have dose adjustments.

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.

Monthly, during the maintenance phase, the investigator completed Parts II (activities of daily living) and III (motor exam) of the UPDRS.

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. In order for the study to be declared positive, both primary endpoints had to achieve statistical significance. The ITT population was to be the primary analysis population with an LOCF technique employed for missing data.

Pramipexole Ascending-Dose Schedule

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

APPEARS THIS WAY
ON ORIGINAL

A stated secondary endpoint for the study was time-to-failure where failure was defined as requiring treatment with L-dopa.

Subset analyses were also planned based on concomitant use of l-deprenyl and anticholinergic medications.

The sample size was computed using results in the DATATOP 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.

335 patients were randomized: 164 pramipexole and 171 placebo. The investigators and centers are listed at the end of this Study 1 review.

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

	Placebo N=171	Pramipexole N=164
Age	62	63
Sex	98M/73F	105M/59F
Race	94% White	95% White
Parkinson's Duration	1.7 yrs	2 yrs
Deprenyl Use	66%	68%
Anticholinergic Use	14%	12%
Part II Score	8	8
Part III Score	18.7	18.8
Hoehn & Yahr	1.9	1.9

Patient Flow: Only 2 patients (1 in each treatment group) did not meet the ITT definition, i.e. they did not have at least one efficacy assessment. Therefore, 333 patients are included in the efficacy analysis: 163 pramipexole and 170 placebo.

The following table outlines the withdrawals during the study.

Withdrawals

	Pramipexole	Placebo
Ascending Dose Phase	12	10
Maintenance Phase	16	24
TOTAL	28	34
	62	

The reasons for withdrawals are shown in the next table.

Patient Disposition

	Pramipexole	Placebo
Disease Worsening	4	15
Worsening of Pre-existing Disease	0	1
Other AEs	18	8
Poor Therapeutic Resp.	1	7
Protocol Violation	1	0
Lost to Follow-Up	2	0
Withdrew Consent	2	2
Other	0	1

136/164 pramipexole patients completed the trial. 137/171 placebo patients completed the trial.

C. Efficacy Evaluation

All the analyses below are LOCF analyses, unless specifically described otherwise.

There were 2 patients who received drug but did not have any post-baseline efficacy measurements (1 patient per treatment group). Thus, 333 patients (163 pramipexole, 170 placebo) comprise the ITT population.

1. UPDRS Part II

Sponsor's Table 5 on the next page shows the average Part II 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.

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.

APPEARS THIS WAY ON ORIGINAL

	LOCF Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-1.9	-57
Placebo	0.4	-5
p-value	$\leq$ 0.0001	$\leq$ 0.0001

APPEARS THIS WAY ON ORIGINAL

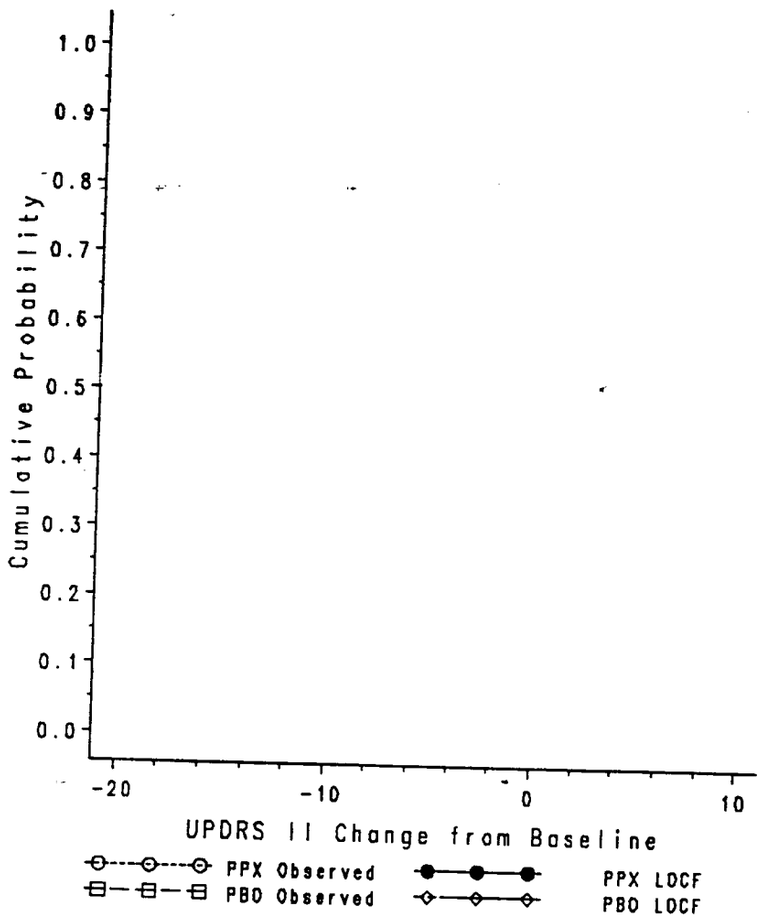
Table 5. Adjusted[a] Mean Change from Baseline in UPDRS Part II Total Score[b], Maintenance Interval
Intent-to-Treat – All Patients, LOCF

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

Source: Appendix C: Table 9.2.

a Adjusted by investigator and investigator-by-treatment interaction.
b Sum of 13 components of UPDRS Part II.
c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
d Week 0 is the endpoint of the ascending-dose interval.

Figure 1
Ogive Curve of UPDRS II Change from Baseline -- M/2730/0001



APPEARS THIS WAY
ON ORIGINAL

2. UPDRS Part III

Sponsor's Table 6 (next page) shows the average Part III scores by visit for the two treatment groups. Cumulative distribution functions are shown on the page after that.

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.

	LOCF Change from Baseline to Final Maintenance Visit	LOCF Area Under the Curve over Maintenance Visits (Visits 11-18)
Pramipexole	-5	-127
Placebo	0.8	-11
p-value	$\leq$0.0001	$\leq$0.0001

3. Modified Hoehn and Yahr Scale

Sponsor's Table 12 (next page) shows the average scores at the beginning and end of the maintenance period for the two treatment groups.

The sponsor also classified patients as: 1) improved, 2) no change, or 3) worsening. The breakdown of patients according to these classifications is presented in Sponsor's Table 13 (next page).

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.

Table 6. Adjusted[a] Mean Change from Baseline in UPDRS Part III Total Score[b], Maintenance Interval
Intent-to-Treat – All Patients, LOCF

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

Source: Appendix C: Table 10.2.

a Adjusted by investigator and investigator-by-treatment interaction.
b Sum of 14 components of UPDRS Part III.
c Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
d Week 0 is the endpoint of the ascending-dose interval.

APPEARS THIS WAY
ON ORIGINAL

Table 12. Summary of the Mean Modified Hoehn and Yahr Scale Classification for All Patients

Mean ± SE	Baseline[a]	Maintenance Week	
		0[b]	24[c]
PPX (N=163)	1.92 ± 0.044	1.77 ± 0.049	1.82 ± 0.052
PBO (N=171)	1.89 ± 0.048	1.83 ± 0.047	1.94 ± 0.05

Source: Appendix C: Table 18A.

a Mean baseline values at Ascending-dose Visit 2 (Ascending Week 1) prior to dosing.
b Week 0 is the endpoint of the ascending-dose interval.
c Last maintenance-dose visit, prior to dose reduction.

APPEARS THIS WAY
ON ORIGINAL

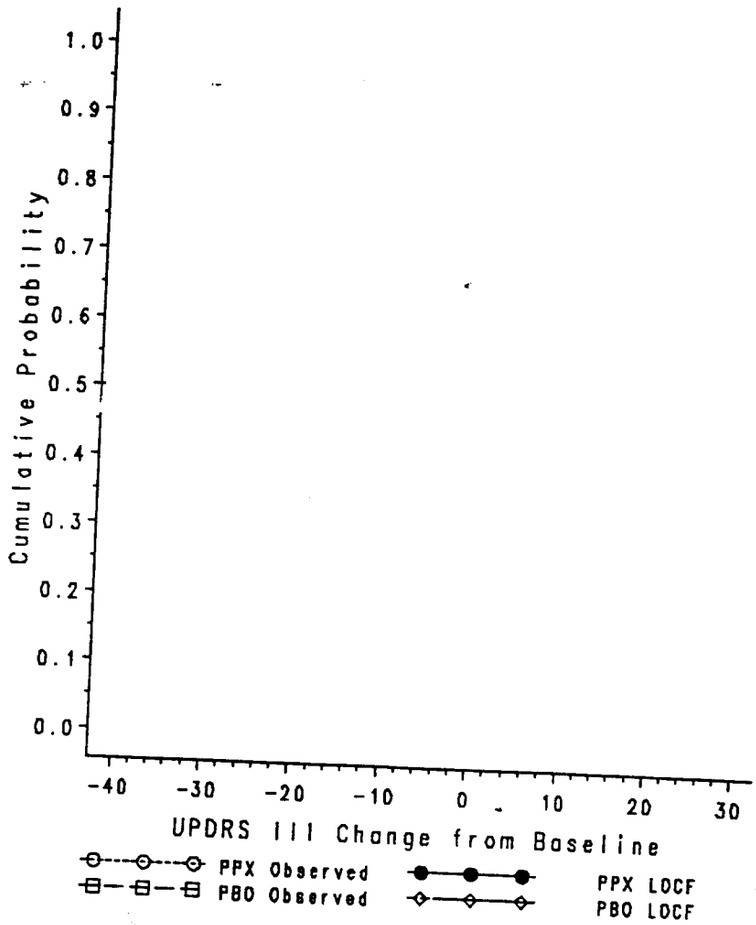
Table 13. Summary of the Change in Modified Hoehn and Yahr Classification from Baseline to Last Maintenance Visit All Patients

Classification Change Based on Modified Hoehn and Yahr Scale	Number (%) of Patients	
	PPX N=161	PBO N=170
Improvement	44 (27.2)	28 (16.5)
No Change	90 (55.6)	102 (60)
Worsening of Classification	27 (16.7)	40 (23.5)

Source: Appendix C: Tables 18A, 19.1A and 19.2A.

APPEARS THIS WAY
ON ORIGINAL

Figure 2
Ogive Curve of UPDRS III Change from Baseline -- M/2730/0001



APPEARS THIS WAY
ON ORIGINAL

E. Subgroup Analyses by Deprenyl and Anticholinergic Use

Sponsor's Table 7 demonstrates that only slight differences in the mean change from baseline for Parts II and III of the UPDRS exist between patients on and off deprenyl. Likewise, only slight differences in these scores exist between patients on and off anticholinergics.

F. Subgroup Analyses by Age, Sex, and Race

Only slight differences in the mean change from baseline for Parts II and III of the UPDRS were shown between male and female patients.

Only 17 patients were non-white so that a subgroup analysis by race is not meaningful.

Only slight differences in the mean change from baseline for Parts II and III of the UPDRS were shown between patients $\geq$ 65 and < 65 years.

Sponsor's Table 8 demonstrates the results of these analyses.

G. Adverse Events

Sponsor's Table 17 shows the AEs with an incidence of 10% or greater in the pramipexole group. Of these, nausea, constipation, asthenia, dizziness, insomnia, somnolence, and hallucinations showed the largest differences between the treatment groups.

There was a single death during the study, a pramipexole patient who had a myocardial infarction and died.

There were 10 pramipexole patients and 12 placebo patients with serious AEs. Most of these were malignancies or cardiac-related. No obvious differences between the treatment groups emerged.

APPEARS THIS WAY
ON ORIGINAL

Table 7. Mean Change From Baseline in UPDRS Parts II and III, Total Score by L-deprenyl and Anti-cholinergic Usage; All Patients

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

Source: Appendix C: Tables 11.1A & 12.1A.
[a] Sum of 13 components of UPDRS Part II.
[b] Sum of 14 components of UPDRS Part III.

APPEARS THIS WAY
ON ORIGINAL

Table 8. Mean Change From Baseline in UPDRS Parts II & III, Total Score by Sex, Age, and Race All Patients

Treatment Group		N	Part II[a]	N	Part III[b]
Age					
<65	PPX	75	-2.0	74	-5.4
	PBO	86	0.1	85	0.6
≥65	PPX	88	-1.6	88	-4.0
	PBO	84	0.7	84	2.2
Sex					
Male	PPX	104	-1.8	103	-5.2
	PBO	97	0.4	97	1.3
Female	PPX	59	-1.9	59	-3.6
	PBO	73	0.3	72	1.4
Race					
White	PPX	156	-1.8	155	-4.7
	PBO	160	0.4	159	1.1
Black	PPX	2	0.5	2	3.5
	PBO	4	-0.8	4	2.0
Other	PPX	5	-2.4	5	-6.0
	PBO	6	1.5	6	7.7

Source: Appendix C: Tables 11.2A and 12.2A.
[a] Sum of 13 components of UPDRS Part II.
[b] Sum of 14 components of UPDRS Part III.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Table 17. Number (%) of Patients With Adverse Events (TES/Reported in ≥10% of the Patients in the Pramipexole Group) by Body System and Adverse Event Regardless of Relationship to Study Medication

Body System Event[a]	Treatment Group[b]	
	PPX (N=164)	PBO (N=171)
	No. Pts (%)	No. Pts (%)
Body as a Whole		
Infection	44 (26.83)	45 (26.32)
Pain	33 (20.12)	35 (20.47)
Asthenia	31 (18.90)	19 (11.11)
Headache	27 (16.46)	31 (18.13)
Pain back	22 (13.41)	17 (9.94)
Injury accident	21 (12.80)	18 (10.53)
Digestive System		
Nausea	64 (39.02)	35 (20.47)
Constipation	29 (17.68)	11 (6.43)
Dyspepsia	18 (10.98)	12 (7.02)
Nervous System		
Dizziness	57 (34.76)	45 (26.32)
Insomnia	42 (25.61)	22 (12.87)
Somnolence	30 (18.29)	15 (8.77)
Tremor	20 (12.20)	34 (19.88)
Hallucinations	18 (10.98)	5 (2.92)

Source: Appendix C: Table 21.1.

a COSTART coding system using preferred term.

b Number of patients in each treatment group is the number randomized who received at least one dose of study drug.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

H. 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.

The sponsor has shown that the effect was present whether or not concomitant deprenyl and anticholinergic medication were used.

The sponsor has also shown that age (above or below 65 years) and sex do not influence response greatly.

APPEARS THIS WAY
ON ORIGINAL

Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Aminoff, Michael J, M.D. Department of Neurology, Rm. M348 University of California San Francisco San Francisco, CA 94143-0216	7
Bennett, James P, Jr., M.D., Ph.D. Fontaine Research Park Neurology Suite 370 500 Ray C. Hunt Drive Charlottesville, VA 22903	13
Burch, Gordon, M.D. Roanoke Neurological Associates 2601 Franklin Road, S.W., Suite B Roanoke, VA 24014-1049	14
Factor, Stewart A., D.O. Professor of Neurology Department of Neurology (A70) Albany Medical Center New Scotland Avenue Albany, NY 12208	14
Farmer, Stephen, D.O. Grayline Clinical Drug Trials 706 Denver Street Wichita Falls, TX 76301	8
Fazzini, Enrico, D.O., Ph.D. 530 First Avenue 9th Floor, Suite 9Q New York, NY 10016	9
Friedman, Joseph, M.D. Department of Neurology Roger Williams General Hospital 50 Maude Street, 4th Floor Providence, RI 02908	15
Golbe, Lawrence I., M.D. UMDNJ Robert Wood Johnson Medical School Dept. of Neurology, 4th Floor 1 Robert Wood Johnson Plaza, CN-19 New Brunswick, NJ 08903-0019	17

Protocol M/2730/0001	
Investigator Name and Address	Number of Patients Randomized at Site
Hill, Thomas, M.D. Center for Clinical Research 911 West 38th Street, Suite 301 Austin, TX 78705	11
Hiner, Bradley, M.D. Marshfield Clinic 1000 North Oak Avenue Marshfield, WI 54449-5777	17
Hoehn, Margaret M., M.D. 3535 Cherry Creek North Drive, #303 Denver, CO 80209	8
Hubble, Jean, M.D. Department of Neurology Kansas University Medical Center 39th and Rainbow Blvd. Kansas City, KS 66103	13
Karp, Jeffrey, M.D. Mease Clinic 3253 McMullen Booth Road, Suite 200 Clearwater, FL 34621-2010	10
Kurth, Matthias, M.D. St. Joseph Hospital Barrow Neurological Institute 222 W. Thomas Road, Suite 401 Phoenix, AZ 85013	25
LeWitt, Peter, M.D. Professional Village Clinical Neuroscience Center 5821 West Maple Road, Suite 192 West Bloomfield, MI 48322	14
Nathan, Denis, M.D. Neurological Consultants, S.C. 2002 W. Howard Avenue Milwaukee, WI 53221	11

Protocol M/2730/0001	
Investigator Name and Address	**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	15
Paulson, George, M.D. Chairman, Department of Neurology 452 Means Hall Ohio State Univ. School of Medicine 1655 Upham Drive Columbus, OH 43210	9
Richter, Ralph W., M.D. St. John's Doctor's Bldg. 1705 E. 19th Street, Suite 406 Tulsa, OK 74104	6
Shannon, Kathleen, M.D. Dept. of Neurological Sciences Rush Medical Center Rush Presbyterian St. Luke's Medical Center 1725 West Harrison, Suite 1106 Chicago, IL 60612	13
Siemers, Eric, M.D. Univ. of Indiana School of Medicine Dept. of Neurology, RG6 Regen Strief Health Center 1050 Walnut, 6th Floor Indianapolis, IN 46202	14
Tetrud, James, M.D. Parkinson's Institute 1170 Morse Avenue Sunnyvale, CA 94089-1605	14

Protocol M/2730/0001	
Investigator Name and Address	**Number of Patients Randomized at Site**
Truong, Daniel R., M.D. Parkinson & Movement Disorders University of California, Irvine College of Medicine Department of Neurology 154 Med. Surge I Irvine, CA 92717	14
Tuchman, Michael M., M.D. Palm Beach Neurological Group 3365 Burns Road - Suite 206 Palm Beach Gardens, FL 33410	17
Watts, Ray L., M.D. Emory University School of Medicine 6000 Woodruff Memorial Bldg. P.O. Drawer V Atlanta, GA 30322	15
Weiner, William, M.D. 1501 N.w. 9th Avenue Parkinson Bldg. Department o Neurology Miami, FL 33136	12

APPEARS THIS WAY
ON ORIGINAL

Study 4

A. Study Design

This was a multicenter, randomized, double-blind, placebo-controlled parallel group study of 4 different fixed doses of pramipexole and placebo. Randomization was stratified for l-deprenyl use.

The treatment periods incorporated an ascending dose period (as long as 6 weeks) followed by a fixed-dose maintenance period of 4 weeks (and a 1-week dose-reduction period).

250 patients were to be entered, 50 per treatment group. A total of 20 centers in the U.S. and Canada were planned with at least 10 patients per center.

The study was conducted by the
After the study was complete, data sets were provided to the Upjohn Company by the

Inclusion criteria were:

Patients with idiopathic Parkinson's disease of less than 7 years duration, Hoehn and Yahr Scale scores of I-III, age 30 years and older. Patients could not have taken L-dopa within the past 3 months.

Deprenyl, anticholinergics, or amantadine therapy at a stable dose for 30 days prior to the study and throughout the study were allowed.

Exclusion criteria were:

1. L-dopa or dopamine agonist medication in previous 3 months.

2. Atypical parkinsonian syndromes, to include drug-induced parkinsonian syndromes.

3. Dementia or active psychosis.

4. Third degree AV block or sick sinus syndrome; CHF Class III or IV; MI

within 6 months.

5. Occurrence of a seizure within 1 year.

6. Renal or hepatic impairment. Neoplastic disease.

7. Symptomatic orthostatic hypotension at screening.

8. History of stereotactic brain surgery.

14. 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, patients were **randomized** to receive the first dose of study medication. An **ascending-dose phase** followed and could last as long as 6 weeks. If patients experienced dose-limiting toxicity prior to reaching their target dose, they could be lowered to the previous dose level. The protocol allowed patients to be lowered only 1 or 2 dose levels. Once lowered to a given level, patients were not to be re-challenged at the higher dose level.

The **maintenance phase** was to last 1 month or 4 weeks. This 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.

The protocol states that concomitant deprenyl, amantadine, or anticholinergics could be used, but at a "stable dosage." This implies that changes in dosage of these drugs during the trial would not be allowed.

Patients were seen every 2 weeks during dose-escalation and during maintenance, for a total of 5 scheduled visits post-randomization. At each visit, the following were performed:

1. UPDRS, Parts I-III
2. Supine and standing BP and pulse
3. Adverse events

APPENDIX E
SCHEDULE OF ACTIVITIES

	Visit Name		Escalation			Maintenance		Taper
	Screen (14 days)	Baseline (Day 0)	Day 14 (week 2)	Day 28 (week 4)	Day 42 (week 6)	Day 56 (week 8)	Day 70 (week 10)	Day 77 (week 11)
Visit #	1	2	3	4	5	6	7	8
Med/Neuro History	x							
Physical Exam	x							
12-lead EKG	x							
Hoehn/Yahr	x	x					x	
Safety Labs	x						x	
UPDRS I-III		x	x	x	x	x	x	x*
Vital Signs		x	x	x	x	x	x	x
NIM's	x	x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x	x
Pharmacokinetics					x		x	
QOL		x					x	
Drug Dispensing		x	x	x	x	x	x	
Compliance Check			x	x	x	x	x	x

*repeat Day 70 abnormal labs

Escalating Pramipexole Dose Schedule

Dose Group	Pramipexole dose - mg/day					
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Placebo	pbo	pbo	pbo	pbo	pbo	pbo
1.5 mg/day	pbo	pbo	pbo	0.375	0.75	1.5
3.0 mg/day	pbo	pbo	0.375	0.75	1.5	3.0
4.5 mg/day	pbo	0.375	0.75	1.5	3.0	4.5
6.0 mg/day	0.375	0.75	1.5	3.0	4.5	6.0

4. Concomitant therapy
5. Safety labs
6. PK blood sample
7. Medication compliance (tablet counts)

At the last visit, the Hoehn and Yahr scale, QOL assessment, and an EKG were additionally performed. The QOL assessments were 1) Functional Status Questionnaire (FSQ) with supplemental questions about employment and 2) EuroQol.

The **FSQ** contains 37 questions. It is designed to be self-administered by the subject in about 10 minutes. The questions are then divided into 6 domains:

- o basic ADLs
- o intermediate ADLs
- o social activities
- o mental health
- o quality of interaction
- o work performance

All questions use the previous month as reference (although it was completed at baseline and at end of maintenance--a 2-month timespan). Responses range roughly from 0-6, with some variation. Higher numbers represented better health. Scores within a domain are added and converted to percent of maximal possible.

There were also several additional questions regarding work (normal work hours, work time lost, or employment changes due to disease), which were analyzed separately.

The **EuroQol** contains 6 health-related questions and an analog scale on which patient rate their health state on a scale from 0-100, where 100 is the best possible health state.

The actual QOL scales are provided at the end of this Study 4 review. The protocol states, "For testing of treatment effects, the principal measures will be changes in the FSQ domain scores, the EuroQol utility score [= analog score], and time lost from work in the previous month."

The primary outcome variable was the change from baseline to end-of-maintenance of the sum of Parts I-III of the UPDRS.

The analysis plan stated that both linear and nonlinear regression models would be considered. "For analyzing efficacy and safety variables, there will be two analyses, one in which the independent variable will be the dose assigned by randomization, and a second analysis in which the actual dose received will be used rather than the dose level to which the subject was randomized."

Subset analyses were not specifically planned based on concomitant use of l-deprenyl, amantadine, and anticholinergic medications.

The sample size was computed using tolerability data from a previous pramipexole trial in which 30% of patients in the 4.5 mg/day group could not tolerate the target dose, while 4% of patients in the placebo group could not tolerate the target dose. With 50 patients per group in the current study, the study was powered to detect a similar difference.

The study was also powered at 0.97 to declare that a dose-response slope of 1.81 was different from zero. The smallest slope that could be detected with a power of at least

B. Subject Disposition and Baseline Comparison

The planned enrollment was 250.

264 patients were randomized as below. The investigators and centers are listed at the end of this Study 4 review.

Baseline Characteristics: No significant differences in the two treatment groups were detected at baseline in demographics or disease characteristics as shown on the next page.

In addition the data on concomitant deprenyl use, amantidine use varied between for the different treatment groups. Anticholinergic use (benzatropine or trihexyphenidyl) varied

Patient Flow: The reasons for withdrawals are shown on the next page. Most of the discontinuations occurred during the ascending dose interval (19 of 26).

APPEARS THIS WAY
ON ORIGINAL

SELECTED DEMOGRAPHIC AND BASELINE FACTORS

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

REASONS FOR STUDY DRUG DISCONTINUATION - NUMBER PATIENTS

Reason	Pramipexole - assigned dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
worsening PD	2	0	0	0	0
worsening other disease	1	0	0	0	0
other adverse event	7	0	4	8	0
administrative*	0	2	0	1	1
Total	10	2	4	9	1

PATIENT DISPOSTION AND TOLERABILITY - NUMBER PATIENTS (%)

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

C. Efficacy Evaluation

Only one patient was not included in the ITT analysis. This patient did not have any post-baseline efficacy assessments.

1. UPDRS Total Score Change From Baseline

The first table on the next page shows the change from baseline in total score for each of the dose groups **as assigned by the randomization scheme.** All groups had significant improvements compared to placebo, but no dose response relationship was apparent.

APPEARS THIS WAY
ON ORIGINAL

The second table on the next page shows the same change from baseline data for each of the dose groups, **but the dose groups are determined by actual dose received.** Again, all groups had significant improvements compared to placebo, but no dose response relationship was apparent.

APPEARS THIS WAY
ON ORIGINAL

Regression analysis (the primary analysis plan stated in the protocol) showed that the coefficient of the linear term was statistically significantly different from zero and the coefficient of the quadratic term was marginally significant from zero for the "assigned group" analysis. Both coefficients were statistically significantly different from zero for the "actual dose received" analysis. The presence of the quadratic term indicates a lack of a linear dose response relationship for both "assigned group" and "actual dose group" analyses. The third table on the next page summarizes these results.

APPEARS THIS WAY
ON ORIGINAL

UPDRS TOTAL SCORE CHANGE FROM BASELINE

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

APPEARS THIS WAY
ON ORIGINAL

UPDRS TOTAL SCORE CHANGE FROM BASELINE

Parameter	Pramipexole - Actual Dose				Placebo n=60
	1.5 mg/day n=57	3.0 mg/day n=53	4.5 mg/day n=50	6.0 mg/day n=43	
baseline	28.7	28.9	27.0	32.6	29.2
mean change*	-6.5	-5.7	-7.7	-7.5	-0.4
pairwise p value vs placebo	0.0001	0.0005	0.0001	0.0001	–
overall p value	0.0001	–	–	–	–

APPEARS THIS WAY
ON ORIGINAL

UPDRS TOTAL SCORE REGRESSION ANALYSIS

Analysis	n	Linear Parameter Estimate	p value	Quadratic parameter estimate	p value
assigned dose group	263	-2.412	0.0296	0.252	0.0537
actual dose received	263	-2.974	0.0054	0.361	0.0056

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

2. Subgroup Analyses

No qualitative interactions were present for pramipexole effects for subgroups of concomitant **selegiline** therapy. The sponsor's analysis of pramipexole effect by **anticholinergic** therapy is flawed because (as acknowledged by the sponsor on page 331 of the Integrated Summary of Efficacy) deprenyl was inadvertently classified as an anticholinergic agent. No analysis of pramipexole effect by **amantadine** use is presented.

Also, no qualitative interactions were present for pramipexole effects for subgroups based on age (<65 years vs. ≥65 years), sex, race (caucasian vs noncaucasian) , or baseline Hoehn-Yahr score. Since very few patients were noncaucasian, no meaningful comparison of responses by race can be made.

3. Secondary Efficacy Variables

UPDRS Part I scores were low at baseline and therefore did not contribute much to the change in total UPDRS.

UPDRS Parts II and III scores each showed a similar pattern of change as the total UPDRS scores (see next page). Cumulative distribution functions for Parts II and III, separately, are on the following pages.

The Hoehn and Yahr data is also shown on the next page, expressed as mean scores as well as percent change.

APPEARS THIS WAY
ON ORIGINAL

UPDRS PART II - CHANGE FROM BASELINE

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

*Adjusted for center and treatment by center interaction
**N.D. - not done since overall p value not significant
Source - Appendix D, Table 11.2A

UPDRS PART III - CHANGE FROM BASELINE

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

*Adjusted for center and treatment by center interaction
Source - Appendix D, Table 12.2A

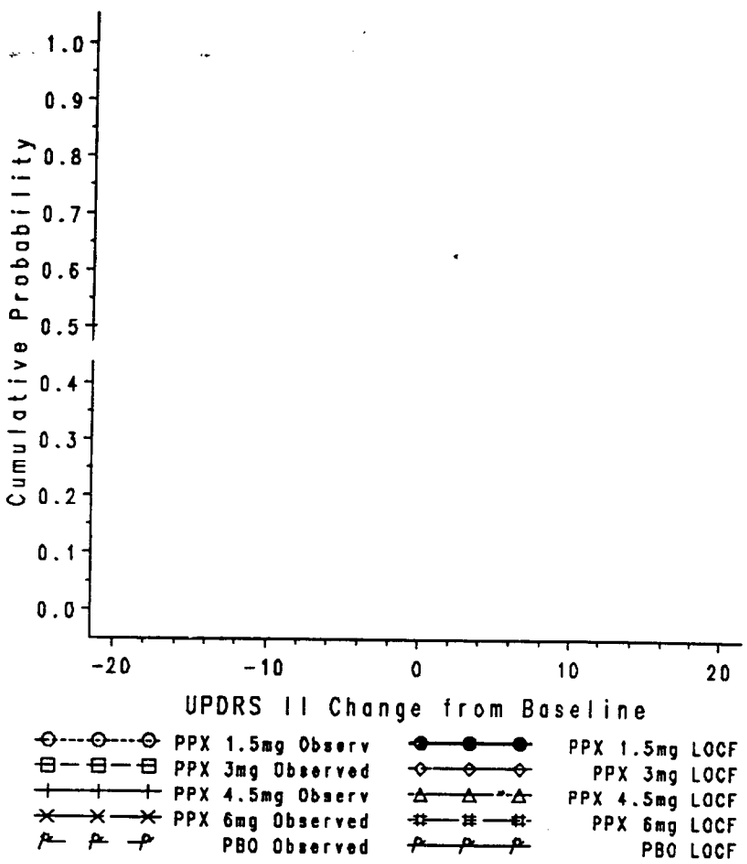
MODIFIED HOEHN AND YAHR SCALE - MEAN SCORES

Item	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
baseline	1.77	1.92	1.81	1.86	1.79
end maintenance	1.74	1.70	1.68	1.74	1.87

MODIFIED HOEHN AND YAHR SCALE - PERCENT CHANGE

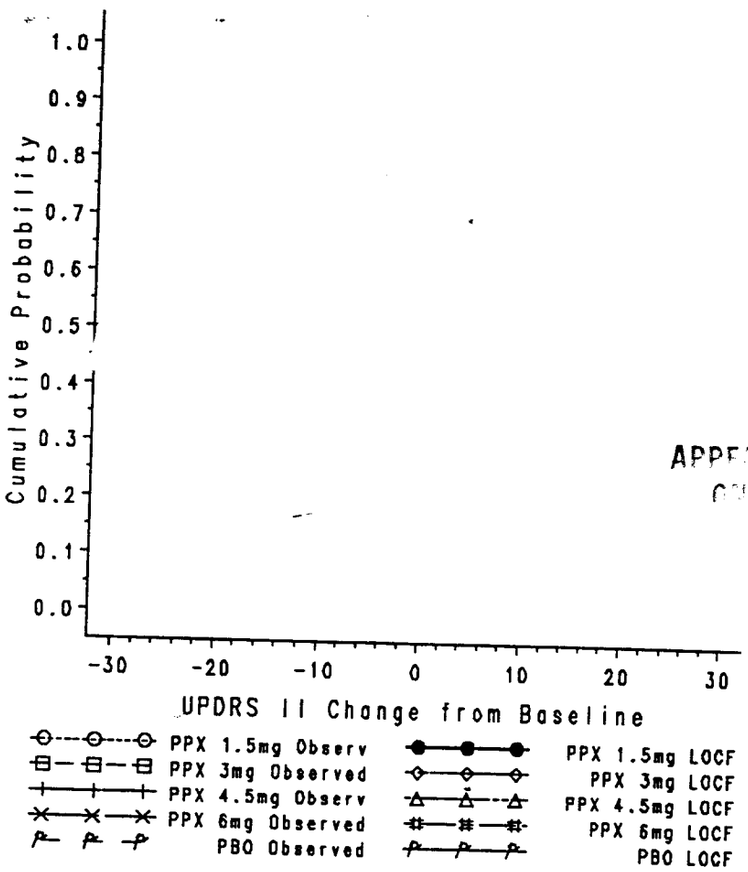
Category	Pramipexole - Assigned Dose				Placebo
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day	
improved from baseline (%)	19.2	36.7	25.0	30.2	13.7
worsened from baseline (%)	17.3	6.1	5.8	9.4	25.5

Figure 3
Ogive Curve of UPDRS II Change from Baseline -- M/2730/0004



PBO Observed overlaying PBO LOCF because there was no dropouts in PBO

Figure 4
Ogive Curve of UPDRS III Change from Baseline -- M/2730/0004



PBO Observed overlaying PBO LOCF because there was no dropouts in PBO

4. Quality of Life Scales

The sponsor's table on the next page demonstrates mean change from baseline for different scales and components of scales. Responses are present for all but two patients (one in the 1.5 mg group and one in the 4.5 mg group). As a reminder, the scores are all converted to a 0-100 scale with 100 representing a best response. A positive change represents improvement, while a negative change represents worsening.

Note that the overall p-value is significant for only one domain, the FSQ basic ADL. Even for that domain, the magnitude of change is so small, except perhaps for the 1.5 mg/day group, as to be clinically insignificant. The overall p-value for the EuroQol analog scale approached significance (p=0.065), with the 3 mg/day and 4.5 mg/day groups demonstrating the largest differences compared to placebo.

Separately, the sponsor presents correlation coefficients for UPDRS change scores and QOL change scores. They all tended to be low.

APPEARS THIS WAY
ON ORIGINAL

MEAN CHANGES FROM BASELINE FOR QOL SCORES

Domain /item	Pramipexole - assigned dose				Placebo	Overall p-value
	1.5 mg/day	3.0 mg/day	4.5 mg/day	6.0 mg/day		
FSQ-Basic ADL	4.8**	1.6	2.0*	-0.7	-2.6	0.0255
FSQ-Interm. ADL	1.0	3.7	-1.5	-1.5	-0.1	0.1936
FSQ-Mental Health	1.0	2.0	0.1	0.9	1.5	0.9991
FSQ-Work Perf.	0.9	1.3	-1.9	-0.9	0.6	0.7353
FSQ-Social Activity	0.7	0.4	0.0	-1.3	-2.4	0.9836
FSQ-Quality of Interaction	0.1	-0.5	0.9	-0.1	-0.5	0.8629
FSQ-Days (not) in Bed	0.2	0.0	0.0	0.0	0.0	0.8032
FSQ-Days (not) cut down on activities	1.0	0.8	0.5	-0.1	-0.3	0.4150
FSQ-Satis. w/ sexual relations	-0.1	0.0	0.1	0.0	0.0	0.8175
FSQ-Feelings about own health	0.1	0.4	0.2	0.1	0.2	0.1650
FSQ-Freq. of social activity	-0.1	-0.1	0.0	0.2	-0.2	0.2974
EuroQol-Analog	1.4	4.8	4.0	0.7	-2.3	0.0654
No lost work	0.0	0.2	-0.3	-0.2	-0.4	0.4259

**p-value vs. placebo=.0016
* p-value vs. placebo=.0686
Source: Appendix D, Table 18.1