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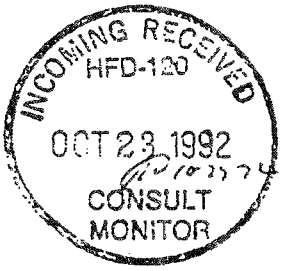
STATISTICAL REVIEW AND EVALUATION



Date: SEP 11 1992

NDA #: 20-031/Drug Class 1-S

Applicant: SmithKline Beecham

Drug: Paxil[1] (paroxetine hydrochloride)

Indication: depression

Documents Reviewed: Volumes 1.450 - 1.476, 1.571 - 1.573, and sponsor's response to requested data dated 27 June 1991.

Medical Input: The initial clinical reviewer for this application was Martin Brecher, M.D., HFD-120.

PAR 01-001, Jay Cohn, Principal Investigator

Study Characteristics

This was a single center, double blind, parallel group, placebo controlled, phase two trial conducted in the United States. Patients were randomized to treatment in blocks of four with a target sample size of 72 patients; a total of 50 patients were actually enrolled. The trial lasted 6 weeks and consisted of a pre-treatment screening visit, a baseline visit, and follow-up visits at 1, 2, 3, 4 and 6 weeks post-baseline. There was a placebo washout phase between the screening and baseline visits that lasted from 4 to 14 days, depending on factors such as the patient's recent use of psychotropic medications. Active treatment began at baseline with the paroxetine subjects receiving a 20mg daily dose. At each subsequent visit the physician could taper the dose up or down by 10mg, so that the final daily dose could range from 10mg to 50mg.

The primary efficacy variable was mean change from baseline in Hamilton Depression (Ham-D) Total at 6 weeks. At the recommendation of the FDA Division of Neuropharmacology, this reviewer also examined the following secondary efficacy measures at week 6: Ham-D Depressed Mood Item, CGI Severity, CGI Global Improvement and Zung Self-Rating Depression Scale Total (the only patient self assessment variable used in this trial). Mean change from baseline at week 6 was analyzed for all secondary efficacy measures except CGI Global Improvement; mean CGI Global Improvement at 6 weeks was examined since a mean change from baseline is not meaningful for a global improvement variable.

Sponsor's Statistical Methods

The sponsor analyzed two populations: the intent-to-treat population, which included all subjects randomized to treatment and who received at least one dose of drug; and the all efficacy population, which was comprised of those in the intent-to-treat population except protocol violators and adverse reactions. Last Observation Carried Forward (LOCF) and visit-wise (observed cases

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[1] Original trade name Arapax

(OC)) analyses were performed on each of the two populations. Only the LOCF and OC analyses on the intent-to-treat population were examined by this reviewer.

The following models were used to describe changes from baseline for the primary and secondary variables:

Model II (Analysis of Variance)
(value - baseline value) = treatment + error;

Model III (Analysis of Covariance)
(value - baseline value)
= treatment + covariable + treatment*covariable + error;

Model IV Method) -- same as model II using the nonparametric CMH method on (Ham-D Depressed Mood Item - baseline Ham-D Depressed Mood Item);

Model V (Analysis of Variance on Ranks) -- same as model II using rank transformation of (Ham-D Total - baseline Ham-D Total).

The sponsor indicated that Ham-D Total was the first outcome examined in the Model III analyses because it was representative of the other outcome variables in the trial. If baseline discrepancies in Ham-D Total across levels of a covariable were found, Model III was then used to examine baseline discrepancies for other outcomes. Model IV was used to nonparametrically analyze Ham-D Depressed Mood Item, an ordinal four point score. If baseline differences for a covariable were apparent, Model IV was adapted to adjust for that covariable after if had been appropriately categorized. Model V was employed on the Ham-D Total only.

For Models II, III and V, the sponsor stated that all reported p-values were computed by comparing least squares, rather than arithmetic, treatment means. They were obtained from SAS using the PDIFF option in the LSMEANS statement of Procedure GLM. All reported p-values were two sided.

The sponsor's models were appropriate and properly estimated. SAS Listings verifying the information provided by the sponsor and reported by this reviewer in Tables 01-001.01 through 02-004.02 (except for the OC analyses of the Ham-D Depressed Mood Item, which were a response to a request by FDA) were found on the VAX computer which housed the sponsor's CANDA.

Sponsor's Results

Table 01-001.01 displays the 6 week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. Paroxetine patients showed greater improvement on all measures in the LOCF analysis and on all but the Zung Total in the OC analysis. Reductions in the Ham-D Total, Ham-D Depressed Mood Item, and CGI Severity were larger for paroxetine patients than placebo patients in the LOCF and OC analyses. Mean CGI Global Improvement was greater among paroxetine patients in the LOCF and OC analyses. Paroxetine patients exhibited a greater reduction in self-reported depressive symptoms than placebo patients in the LOCF analysis; placebo patients, however, exhibited a greater reduction than paroxetine patients in the OC analysis. None of the differences between treatments was statistically significant.

Table 01-001.01. Mean Change from Baseline to Six Weeks
PAR 01-001, Jay Cohn, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep. Var.	Paroxetine Mean	SE	N	Placebo Mean	SE	N	p-value
HamD Tot.	-13.46	1.60	24	-10.54	1.60	24	0.204
HamD Dep.	-1.46	NR	24	-1.12	NR	24	0.187
CGI Sev.	-1.75	0.28	24	-1.33	0.28	24	0.296
CGI G.I.	1.75	0.22	24	2.25	0.22	24	0.113
Zung Tot.	-7.83	2.15	24	-7.21	2.15	24	0.838

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep. Var.	Paroxetine Mean	SE	N	Placebo Mean	SE	N	p-value
HamD Tot.	-15.58	1.51	19	-13.94	1.64	16	0.467
HamD Dep.	-1.68	0.17	19	-1.50	0.19	16	0.461
CGI Sev.	-2.00	0.32	19	-1.81	0.34	16	0.691
CGI G.I.	1.53	0.18	19	1.69	0.20	16	0.548
Zung Tot.	-8.95	2.05	19	-13.19	2.23	16	0.171

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

Since only 67 percent of the placebo patients were still in the trial at week 6, the week 4 results were examined. In the intent-to-treat population at week 4, 79 percent (19/24) of paroxetine patients and 75 percent (18/24) patients remained in the trial. The results at week 4 were all in the same direction as at week 6 but none of the differences was statistically significant.

The mean daily dose of paroxetine at the 6 week endpoint was 39.0 mg/day among the 24 intent-to-treat patients and 38.9 mg/day among the 17 efficacy patients. The mean daily dose for both groups continually increased during the 6 week period.

Reviewer's Comments

The protocol stated the target sample size was 72 patients but only 50 were actually enrolled in the trial. Obviously the power of this trial was lower than planned; this may explain the lack of statistical significance of any of the treatment differences that the sponsor found.

This trial provided no statistical evidence that paroxetine was superior to placebo with regard to the primary and secondary efficacy measures examined.

Introduction

The accompanying safety review contains a brief synopsis of paroxetine's development and details concerning the Phase II-III paroxetine exposure. Appendix A summarizes the demographic data of the efficacy trials.

Efficacy will be assessed by review of each of 17 double blind, placebo controlled randomized trials. Results of 34 active controlled trials will be summarized. Table 1 lists the placebo controlled trials and Appendix B lists the active controlled trials.

In a letter to the sponsor FDA identified 5 efficacy variables of primary interest: Hamilton Depression Scale (HAM-D) total score, HAM-D depression item, HAM-D retardation factor, CGI (Clinical Global Impression) severity score and SCL (Symptom Check List) depression factor.

Last Observation Carried Forward (LOCF) data is referred to in the submission as "extender" data. The sponsor also presented data, labelled "All Efficacy", which excluded data collected within three days of the ingestion of a prescribed medication. The focus of the analysis of efficacy will be on the Intent to Treat population which includes all randomized patients with at least one efficacy evaluation.

The most important assessment points are 4 and 6 weeks after initiation of randomized treatment. In most protocols 70% of the subjects were still in the study after 4 weeks. Practitioners generally allow 4 weeks to determine whether an antidepressant is effective. The pivotal efficacy trials were of 6 week duration.

PLACEBO CONTROLLED TRIALS; U.S. STUDIES

PAR-01-001; Jay Cohen, Principal investigator

This was a six week, one site, randomized, placebo controlled, double blind study of 10-50 mg/d paroxetine versus placebo in moderately to severely depressed outpatients.

Subjects

Subjects met DSM-III criteria for major depression, were 18-65 years of age and had scores of 18 or more on the first 17 items of the HAM-D scale. Exclusion criteria were:

unstabilized renal, hepatic, cardiovascular, respiratory or endocrinological disease,
a history of narrow angle glaucoma, prostatic hypertrophy, seizure, significantly abnormal EKG or allergy to tricyclics,
a primary diagnosis of schizophrenia or atypical depression,
a diagnosis of manic-depressive illness, primary anxiety disorder or adjustment disorder,
concomitant treatment with another psychotropic agent,
a history of drug or alcohol abuse.

a history of ECT within the preceding three months,
use of an investigational drug within the preceding 30 days,
use of a MAOI within 14 days,
use of a psychotropic within the preceding 7 days,
a clinically significant abnormal lab value at screen examination,
known suicidal tendencies,
a decrease of 20% or more between screen exam and baseline exam (placebo responders),
patients with more anxiety than depression as assessed on the Raskin-Covi scale,
women of child bearing potential.

Design

After a one week placebo washout patients were started on 10mg/d paroxetine or placebo. On day 7 patients could be increased to 20 mg/d. From day 14 to day 28 patients could receive 10-50 mg/d. Dosage was fixed after day 28. Efficacy was assessed with the HAM-D, Montgomery-Asberg Depression Rating Scale (MADRS), the Zung Self Rating Scale and the CGI. The week 6 timepoint was the assessment of primary interest. Concomitant psychotropic medication was prohibited except for 500mg chloral hydrate for a maximum of three consecutive nights.

Results

The groups did not differ in their demographic parameters, in the time course of the present episode of depression or their psychiatric histories. The placebo patients were more likely ($p<.01$) to have a family member who drank excessively. 65% of the patients were male and the mean age of the sample was 43.

50 subjects were enrolled, but only 43 were considered by the sponsor to be evaluable. One patient in each group discontinued and 5 patients (2 paroxetine and 3 placebo) used a concomitant medication with potential CNS effects. 32 patients (17 paroxetine and 15 placebo) completed the study.

The mean daily dose of paroxetine in the Intent to Treat sample was 26.7 mg and the mean endpoint dose was 35.0 mg. Paroxetine patients remained in the study for an average of 39.0 days compared to 34.7 days for the placebo patients ($p=.25$). Mean baseline HAM-D scores were 28.0 in the paroxetine sample and 27.4 among patients who received placebo ($p=.61$). Compliance was 95-96% in both groups.

The changes from baseline to Week 6 in the Intent to Treat sample extender data set (LOCF) were:

01-001

Variable	Paroxetine N	Paroxetine Mean (SE)	Placebo N	Placebo Mean (SE)	p
HAM-D Total	24	-13.46 (1.60)	24	-10.54 (1.60)	.204
HAM-D Retardation Factor	24	-3.96 (0.50)	24	-2.58 (0.50)	.056
HAM-D Depressed Mood Item	24	-1.46 ---	24	-1.12 ---	.187+
CGI Severity of Illness	24	-1.75 (0.28)	24	-1.33 (0.28)	296
CGI Global Improvement*	24	1.75 (0.22)	24	2.25 (0.22)	.113
Zung Self Rating Scale	24	-7.83 (2.15)	24	-7.21 (2.15)	.838
MADRS	24	-14.33 (1.71)	24	-11.33 (1.71)	.220

* Lower score indicates greater improvement; + p-value derived from odds ratio

Similar results were obtained when patients who took concomitant psychoactive medications were excluded, when analysis was limited to completers and when non-parametric analysis of the data was performed. Baseline values for the HAM-D Total and 3 of the 4 factor scores were similar in the paroxetine and placebo groups. There was no significant between group difference in HAM-D Total or any of the 4 HAM-D factors at any of the 5 assessment points (Weeks 1, 2, 3, 4 or 6) although at Weeks 3, 4 and 6 all differences favored paroxetine. The same results were observed in the visit-wise analysis with the exception of one non-significant comparison favoring placebo. 50% of the paroxetine patients and 33% of the placebo patients had a 50% or greater improvement at Week 6 (p=0.38).

The paroxetine patients had more psychomotor retardation (p=.02) at baseline, but ANCOVA did not reveal a significant treatment effect at Week 6. In the All Efficacy sample there was a significant (p=.09) interaction of treatment with family history of non-psychotic psychiatric disturbance. Paroxetine patients with a positive family history (N=3) improved by an average of 8.67 points on the HAM-D total compared to a mean 14.38 point improvement in the placebo group (N=8). For patients without this family history the mean improvement was 14.11 points for the paroxetine group (N=19) and 9.46 points for the placebo group (N=13).

Comment

This small study, consistent across data sets, methods of analysis and outcome variables, does not demonstrate paroxetine to be an effective antidepressant. There was a trend favoring paroxetine which did not approach significance. The patients in this trial were somewhat atypical in being predominantly male.

PAR 02-001; Karl Rickels, Principal Investigator

This was a 6 week, single site, double-blind, placebo controlled, randomized, parallel group study of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe depression without mania (DSM-III 296.2 or 296.

Subjects

Inclusion criteria were a DSM-III diagnosis of depression, age of at least 18 years, a HAM-D score of at least 18 on the first 17 items and a Raskin score of at least 8 and greater than the Covi score. As in the first study mania or a fall in HAM-D score of 20% or more between screening and Day 1 were grounds for exclusion. Other exclusionary criteria were the same as in PAR 01-001 except that a history of narrow angle glaucoma and benign prostatic hypertrophy were dropped as exclusionary criteria and women of child bearing potential could be included provided they were using an acceptable method of birth control, had a negative pregnancy test and were not lactating. The exclusion of drug and alcohol abusers was redefined to patients who abused substances within the preceding 6 months.

Method

Subjects were screened [illegible] days before administration of active drug or placebo and they were assessed at baseline and 1, 2, 3, 4 and 6 weeks after medication began. There was a minimum of 7 days of placebo washout for patients who had been receiving psychotropic medication and a 4 day minimum placebo washout for those patients not on psychotropics. The protocol was amended to include an optional 2 week extension for those patients who completed 6 weeks of treatment.

PAR 02-001, Karl Rickels, Principal Investigator

Study Characteristics

This trial's intended design was nearly identical to the design of PAR 01-001. The protocol called for a target sample size of 72 patients in a single center. A total of 111 patients were enrolled in a center containing 9 sub-investigator centers. The original NDA submission contained single center analyses. At the request of the FDA, the sponsor submitted an amendment (volume 1.468.1) which presented multicenter analyses that treated the sub-investigator centers as separate centers. The primary efficacy variable was mean change from baseline in Ham-D Total at 6 weeks. This reviewer examined the secondary efficacy measures Ham-D Depression Item, CGI Severity, CGI Global Improvement, and Patient's Global Evaluation.

Sponsor's Statistical Methods

The sponsor's methods for this trial in the original NDA submission were identical to those employed in PAR 01-001.

In the multicenter amendment, the sponsor presented analysis of covariance models that contained terms for treatment, sub-investigator center and a treatment by sub-investigator center interaction. Three of the 9 sub-investigator centers were collapsed into a single center due to small numbers.

Sponsor's Results

Table 02-001.01 displays the six week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. In both the LOCF and OC analyses, subjects receiving paroxetine showed statistically significantly greater improvement than placebo patients on all measures except the Patient's Global Improvement.

Table 02-001.01. Mean Change from Baseline to Six Weeks
PAR 02-001, Karl Rickels, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-12.27	1.33	51	-6.81	1.31	53	0.004
HamD Dep.	-1.39	NR	51	-0.83	NR	53	0.017
CGI Sev.	-1.51	0.20	51	-0.74	0.20	53	0.007
CGI G.I.	2.49	0.22	51	3.23	0.22	53	0.019
Pat. G.E.	-0.98	0.20	51	-0.69	0.20	51	0.306

Table 02-001.01. Mean Change from Baseline to Six Weeks
PAR 02-001, Karl Rickels, Principal Investigator (cont'd)

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-14.29	1.53	38	-8.78	1.55	37	0.014
HamD Dep.	-1.79	0.17	38	-1.03	0.18	37	0.003
CGI Sev.	-1.84	0.23	38	-0.97	0.23	37	0.010
CGI G.I.	2.16	0.24	38	2.89	0.25	37	0.038
Pat. G.E.	-1.26	0.23	38	-0.94	0.24	35	0.332

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

In the multicenter amendment, the sponsor first explored baseline comparability in the LOCF data using an analysis of covariance model that contained terms for treatment, sub-investigator center, and a treatment by sub-investigator center interaction. Recall that 3 of the 9 sub-investigator centers were collapsed due to small frequencies. Statistically significant ($p<0.10$) interaction terms were found for baseline Ham-D Total ($p=0.0038$) and the baseline Ham-D Depressed Mood Item ($p=0.0108$). The sponsor hypothesized that Dr. Clary's subcenter was the source of the interaction. The analyses of baseline Ham-D Total and baseline Ham-D Depressed Mood Item were performed with Dr. Clary's site excluded and the interaction terms were no longer statistically significant (Ham-D Total $p=0.1650$, Ham-D Depressed Mood Item $p=0.1307$), indicating that Dr. Clary's site indeed contributed to the interaction effect.

Improvement from baseline at 6 weeks was next examined using an analysis of covariance model that contained terms for treatment, sub-investigator center, and a treatment by sub-investigator center interaction. The models discussed here were estimated using the LOCF data with Dr. Clary's site excluded.

The LOCF multicenter results were not as impressive as their single center counterparts. A statistically significant interaction was found for improvement in Ham-D Total ($p=0.0069$) but the treatment effect was also significant ($p=0.0200$). This treatment effect was not as strong as in the single center analysis ($p=0.0043$). The model of improvement in Ham-D Depressed Mood Item contained statistically insignificant treatment ($p=0.0968$) and interaction ($p=0.0859$) effects. In the model of improvement in CGI Severity, the treatment effect was statistically significant ($p=0.0482$) but the interaction was not ($p=0.0848$). As with Ham-D Total, however, this treatment effect was less compelling than in the single center analysis ($p=0.0069$).

Treatment by center means (LOCF data) for Ham-D Total, Ham-D Depressed Mood Item, and CGI Severity are displayed in appended Figures 1-3. For all three variables, treatment reversals (i.e. less improvement among paroxetine than placebo patients) were evident for the sites denoted "Schweizer" and "Other."

Since the daily dose of paroxetine was not fixed, the sponsor reported dosing information for the observed paroxetine cases in the original NDA submission. Among intent-to-treat patients, the mean daily dose at week 6 was 39.5 mg/day (38.5 among efficacy patients); the daily dose steadily increased from baseline to week 6.

Reviewer's Comments

The results of the single center analyses indicated paroxetine was far superior to placebo. The multicenter results, however, painted a weaker and incomplete picture.

The multicenter analysis of covariance showed treatment effects for Ham-D Total and CGI Severity that barely surpassed the alpha=0.05 criterion for statistical significance. Further detracting from the evidence of paroxetine's superiority to placebo was the lack of statistical significance for the treatment effect in the Ham-D Depressed Mood Item model. The strong statistical interaction found in the model of Ham-D Total, despite having deleted the site that appeared to be the major source of baseline noncomparability, indicated the presence of treatment reversals that made an interpretation of this analysis difficult. The fact that the same sites displayed treatment reversals for Ham-D Total, Ham-D Depressed Mood Item and CGI Severity indicated a consistent discrepancy in the use of these scales across sites. It could only be concluded that investigators were not employing the Ham-D and CGI in a standardized fashion across subcenters.

PAR 02-002, James Claghorn, Principal Investigator

Study Characteristics

Trial PAR 02-002 used a design virtually identical to that of PAR 02-001. The target sample size was 72 patients and 72 patients were enrolled.

Sponsor's Statistical Methods

The methods used in this trial were identical to those employed in trials PAR 02-001 and PAR 01-001.

Sponsor's Results

Table 02-002.01 displays the 6 week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. In the LOCF analysis, paroxetine patients' improvement was statistically significantly superior to placebo patients' improvement on all measures except Patient's Global Evaluation. In the OC analysis, reductions in Ham-D Total, CGI Severity, CGI Global Improvement and Patient's Global Evaluation were larger for paroxetine patients but statistically insignificant; the only statistically significant reduction for paroxetine patients was on the Depressed Mood Item.

Less than 70 percent of placebo patients remained in the trial at week 6. Table 02-002.02 shows the 4 week results. The results of the 4 week LOCF analysis, where both treatments had greater than 70 percent of patients remaining in the trial, differed from the 6 week analysis in that neither Ham-D Total nor Patient's Global Evaluation was statistically significantly lower for paroxetine patients. In the 4 week OC analysis, CGI Severity and CGI Global Improvement were statistically significantly lower for paroxetine where at 6 weeks they were not.

Similar results were obtained when patients who took concomitant psychoactive medications were excluded, when analysis was limited to completers [redacted] when non-parametric analysis of the data was performed. Baseline values [redacted] the HAM-D Total and 3 of the 4 factor scores were similar in the paroxetine and placebo groups. There was no significant between group difference [redacted] HAM-D Total or any of the 4 HAM-D factors at any of the 5 assessment points (Weeks 1, 2, 3, 4 or 6) although at Weeks 3, 4 and 6 all differences favored paroxetine. The same results were observed in the visit-wise analysis [redacted] with the exception of one non-significant comparison favoring placebo. 50% [redacted] the paroxetine patients and 33% of the placebo patients had a 50% or greater improvement at Week 6 (p=0.38).

The paroxetine patients had more psychomotor retardation (p=.02) at baseline, but ANCOVA did not reveal a significant treatment effect at Week 6. In the All Efficacy sample there was a significant (p=.09) interaction of treatment with family history of non-psychotic psychiatric disturbance. Paroxetine patients with a positive family history (N=3) improved by an average of 8.67 points on the HAM-D total compared to a mean 14.38 point improvement in the placebo group (N=8). For patients without this family history the mean improvement was 14.11 points for the paroxetine group (N=19) and 9.46 points for the placebo group (N=13).

Comment

This [redacted] study, consistent across data sets, methods of analysis and outcome variables, does not demonstrate paroxetine to be an effective antidepressant. There was a trend favoring paroxetine which did not approach significance. The patients in this trial were somewhat atypical in being predominantly male.

PAR 02-001; Karl Rickels, Principal Investigator

This was a 6 week, single site, double-blind, placebo controlled, randomized, parallel group study of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe depression without mania (DSM-III 296.2 or 296.3).

Subjects

Inclusion criteria were a DSM-III diagnosis of depression, age of at least 18 years, a HAM-D score of at least 18 on the first 17 items and a Raskin score of at least 8 and greater than the Covi score. As in the first study mania or a fall in HAM-D score of 20% or more between screening and Day 1 were grounds for exclusion. Other exclusionary criteria were the same as in PAR 01-001 except that a history of narrow angle glaucoma and benign prostatic hypertrophy were dropped as exclusionary criteria and women of child bearing potential could be included provided they were using an accepted method of birth control, had a negative pregnancy test and were not lactating. The exclusion of drug and alcohol abusers was redefined to patients who abused substances within the preceding 6 months.

Method

Subjects were screened 4-14 days before administration of active drug or placebo and they were assessed at baseline and 1, 2, 3, 4 and 6 weeks after medication began. There was a minimum of 7 days of placebo washout for patients who had been receiving psychotropic medication and a 4 day minimum placebo washout for those patients not on psychotropics. The protocol was amended to include an optional 6 week extension for those patients who completed 6 weeks of treatment.

These patients were assessed at 9 and 12 weeks.

Medication was taken in the morning. The dose of paroxetine was: week 1- 20mg; week 2- 10-30mg; weeks 3-6 10-50mg.

All concomitant psychotropic medication was prohibited except for 500mg chloral hydrate for a maximum of 4 consecutive nights during the period between the screening evaluation and Day 7. An individual visit was excluded from the analysis if a drug with a potential CNS effect (centrally active antihypertensive, analgesic or muscle relaxant, H_2 blocker, anticholinergic, antihistamine, narcotic, psychotropic or sympathomimetic) was taken within 3 days.

The HAM-D total score at endpoint was the primary efficacy variable. Secondary variables were the HAM-D retardation factor, (MADRS, CGI) Patient's Global Assessment (PGE) and Raskin Total Score.

Results

111 patients were randomized of whom 28 (16 paroxetine and 12 placebo) were considered unevaluable by the sponsor. 21 of the patients considered unevaluable by the sponsor took medication with a potential CNS effect. The randomized patients were 64% female with a mean age of 45 years and a mean HAM-D total baseline score of 26. Efficacy data was available on 104 patients. Among the 104 patients in the Intent to Treat group there were no significant ($p<.05$) between group differences on any baseline demographic variables, features of the current episode, previous psychiatric history, family history, primary diagnosis or secondary diagnosis. 69% of paroxetine patients and 66% of placebo patients completed the study.

The mean daily dose of paroxetine was 30.7 mg and the mean endpoint dose was 34.9 mg. The mean number of days in the study was 35.9 for paroxetine and 34.0 for placebo ($p=.51$). Mean baseline HAM-D was 25.6 in the paroxetine group and 25.9 in the placebo group ($p=.47$). Compliance was >90% in both groups.

The changes from baseline to Week 6 on the primary (HAM-D total) and secondary variables for the Intent to ~~Treat~~ (ITT) and Evaluable (ALL Efficacy) samples determined by Last Observation Carried Forward (LOCF) were:

	INTENT TO TREAT				
	Paroxetine		Placebo		
Variable	n	mean (S.E.)	n	mean (S.E.)	p-value
HAM-D Total	51	-12.27 (1.33)	53	-6.81 (1.31)	0.004
HAM-D Depressed Mood Item	51	-1.39 ---	53	-0.83 ---	0.017
HAM-D Retardation Factor	51	-3.57 (0.43)	53	-2.06 (0.42)	0.014
Raskin Total	51	-3.88 (0.42)	53	-2.26 (0.42)	0.008
(CGI) Severity of Illness	51	-1.51 (0.20)	53	-0.74 (0.20)	0.007
(CGI) Global Improvement	51	2.49 (0.22)	53	3.23 (0.22)	0.019
Patient's Global Evaluation	51	-0.98 (0.20)	51	-0.69 (0.20)	0.306

	EVALUABLE PATIENTS				
	Paroxetine		Placebo		
Variable	n	mean (S.E.)	n	mean (S.E.)	p-value
HAM-D Total	39	-14.67 (1.41)	44	-8.25 (1.32)	0.001
HAM-D Depressed Mood Item	39	-1.69 ---	44	-0.93 ---	0.003
HAM-D Retardation Factor	39	-4.44 (0.45)	44	-2.52 (0.43)	0.003
Raskin Total	39	-4.49 (0.45)	44	-2.59 (0.43)	0.003
CGI Severity of Illness	39	-1.85 (0.22)	44	-0.84 (0.20)	0.001
CGI Global Improvement	39	2.15 (0.22)	44	3.05 (0.21)	0.005
Patient's Global Evaluation	39	- 1.21 (0.22)	42	-0 69 (0.21)	0.099

In the Intent to Treat sample LOCF analysis of HAM-D total scores a significant treatment effect favoring paroxetine was observed at week 2 which was sustained through week 6. In the visit wise analysis a significant effect favoring paroxetine emerged at 4 weeks and was present at the 6 week endpoint. In the LOCF analysis a significant (p=.017) paroxetine advantage on the depressed mood item emerged at week 6 which was not present at week 4. (Visit-wise data was not presented). LOCF and visit-wise analyses of the Raskin scale data showed paroxetine superior to placebo at week 6, but the effect was not significant at earlier assessments. In both LOCF and visit-wise analyses the CGI Severity of Illness and Global Improvement scores showed a significant paroxetine advantage at weeks 4 and 6.

49% of paroxetine patients and 22% of placebo patients improved by at least 50% ($p<.01$).

Analysis of the data for the evaluable patients was entirely consistent with the results in the Intent to Treat sample. ANCOVA performed on the All Efficacy data set with HAM-D total as the dependent variable did not reveal any significant ($p<.10$) covariate by treatment interactions. The covariates were sex, race, age, marital status, current condition, onset of present episode, duration of present episode, precipitating external event, episode characterization, current treatment status, previous psychiatric treatment, socioeconomic status and highest level of adaptive functioning in the past year.

Comment

This trial demonstrates superiority for paroxetine over placebo in the treatment of moderately depressed outpatients. In the paroxetine group baseline Ham-D total scores of 26 decreased to 14 representing on the one hand a near 50% improvement. However the average patient had significant depressive symptomatology at the Week 6 endpoint.

PAR 02-002; James Claghorn, Principal Investigator

This was a 6 week, single site, double-blind, [redacted] controlled, randomized, parallel group study of paroxetine 10-50 [redacted] outpatients with moderate to moderately severe major depressive [redacted] without mania (DSM-III 296.2 or 296.3).

Subjects

The protocol call[redacted] the random assignment to either paroxetine or placebo of 72 subjects [redacted] pleted the placebo washout. Inclusion criteria were the same

Reviewer's Comments

The results of the single center analyses indicated paroxetine was far superior to placebo. The multicenter results, however, painted a weaker and incomplete picture.

The multicenter analysis of covariance showed treatment effects for Ham-D Total and CGI Severity that barely surpassed the alpha=0.05 criterion for statistical significance. Further detracting from the evidence of paroxetine's superiority to placebo was the lack of statistical significance for the treatment effect in the Ham-D Depressed Mood Item model. The strong statistical interaction found in the model of Ham-D Total, despite having deleted the site that appeared to be the major source of baseline noncomparability, indicated the presence of treatment reversals that made an interpretation of this analysis difficult. The fact that the same sites displayed treatment reversals for Ham-D Total, Ham-D Depressed Mood Item and CGI Severity indicated a consistent discrepancy in the use of these scales across sites. It could only be concluded that investigators were not employing the Ham-D and CGI in a standardized fashion across subcenters.

PAR 02-002, James Claghorn, Principal Investigator

Study Characteristics

Trial PAR 02-002 used a design virtually identical to that of PAR 02-001. The target sample size was 72 patients and 72 patients were enrolled.

Sponsor's Statistical Methods

The methods used in this trial were identical to those employed in trials PAR 02-001 and PAR 01-001.

Sponsor's Results

Table 02-002.01 displays the 6 week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. In the LOCF analysis, paroxetine patients' improvement was statistically significantly superior to placebo patients' improvement on all measures except Patient's Global Evaluation. In the OC analysis, reductions in Ham-D Total, CGI Severity, CGI Global Improvement and Patient's Global Evaluation were larger for paroxetine patients but statistically insignificant; the only statistically significant reduction for paroxetine patients was on the Depressed Mood Item.

Less than 70 percent of placebo patients remained in the trial at week 6. Table 02-002.02 shows the 4 week results. The results of the 4 week LOCF analysis, where both treatments had greater than 70 percent of patients remaining in the trial, differed from the 6 week analysis in that neither Ham-D Total nor Patient's Global Evaluation was statistically significantly lower for paroxetine patients. In the 4 week OC analysis, CGI Severity and CGI Global Improvement were statistically significantly lower for paroxetine where at 6 weeks they were not.

Table 02-002.01. Mean Change from Baseline to Six Weeks
PAR 02-002, James Claghorn, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-10.94	1.44	36	-5.77	1.48	34	0.015
HamD Dep.	-1.19	NR	36	-0.50	NR	34	0.007
CGI Sev.	-1.06	0.17	36	-0.47	0.18	34	0.022
CGI G.I.	2.58	0.19	36	3.38	0.20	34	0.006
Pat. G.E.	-0.92	0.23	36	-0.38	0.24	34	0.114

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-12.48	1.72	25	-7.82	1.83	22	0.070
HamD Dep.	-1.32	0.22	25	-0.59	0.24	22	0.030
CGI Sev.	-1.16	0.22	25	-0.73	0.24	22	0.190
CGI G.I.	2.44	0.24	25	3.05	0.26	22	0.097
Pat. G.E.	-0.72	0.28	25	-0.59	0.30	22	0.757

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

Table 02-002.02. Mean Change from Baseline to Four Weeks
PAR 02-002, James Claghorn, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-10.22	1.36	36	-6.63	1.40	34	0.070
HamD Dep.	-1.14	NR	36	-0.47	NR	34	0.002
CGI Sev.	-1.00	0.15	36	-0.41	0.15	34	0.008
CGI G.I.	2.64	0.17	36	3.38	0.18	34	0.004
Pat. G.E.	-1.03	0.21	36	-0.26	0.21	34	0.012

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-11.28	1.43	28	-8.16	1.45	27	0.132
HamD Dep.	-1.18	0.16	28	-0.56	0.16	27	0.011
CGI Sev.	-1.11	0.16	28	-0.56	0.17	27	0.021
CGI G.I.	2.50	0.18	28	3.15	0.19	27	0.017
Pat. G.E.	-0.89	0.22	28	-0.37	0.23	27	0.105

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

Variable	EVALUABLE PATIENTS Paroxetine n	mean (S.E.)	Placebo n	mean (S.E.)	p value
HAM-D Total	39	-14.67 (1.41)	44	-8.25 (1.32)	0.001
HAM-D Depressed Mood Item	39	-1.69 ---	44	-0.93 ---	0.003
HAM-D Retardation Factor	39	-4.44 (0.45)	44	-2.52 (0.43)	0.003
Raskin Total	39	-4.49 (0.45)	44	-2.59 (0.43)	0.003
CGI Severity of Illness	39	-1.85 (0.22)	44	-0.95 (0.20)	0.001
CGI Global Improvement	39	2.15 (0.22)	44	1.05 (0.21)	0.005
Patient's Global Evaluation	39	- 1.21 (0.22)	42	-0.69 (0.21)	0.099

In the Intent to Treat sample LOCF analysis of HAM-D total scores a significant treatment effect favoring paroxetine was observed at week 2 which was sustained through week 6. In the visit wise analysis a significant effect favoring paroxetine emerged at 4 weeks and was present at the 6 week endpoint. In the LOCF analysis a significant (p=.017) paroxetine advantage on the depressed mood item emerged at week 6 which was not present at week 4. (Visit-wise data was not presented). LOCF and visit-wise analyses of the Raskin scale data showed paroxetine superior to placebo at week 6, but the effect was not significant at earlier assessments. In both LOCF and visit-wise analyses the CGI Severity of Illness and Global Improvement measures showed a significant paroxetine advantage at weeks 4 and 6.

49% of paroxetine patients and 22% of placebo patients improved by at least 50% ($p<.01$).

Analysis of the data for the evaluable patients was entirely consistent with the results in the Intent to Treat sample. ANCOVA performed on the All Efficacy data set with HAM-D total as the dependent variable did not reveal any significant ($p<.10$) covariate by treatment interactions. The covariates were sex, race, age, marital status, current condition, onset of present episode, duration of present episode, precipitating external event, episode characterization, current treatment status, previous psychiatric treatment, socioeconomic status and highest level of adaptive functioning in the past year.

Comments

This trial demonstrates superiority for paroxetine over placebo in the treatment of moderately depressed outpatients. In the paroxetine group baseline Ham-D total scores of 26 decreased to 14 representing on the one hand a near 50% improvement, however the average patient had significant depressive symptomatology at the Week 6 endpoint.

PAR 02-002; **James Claghorn**, Principal Investigator

This was a 6 week, single site, double-blind, placebo controlled, randomized, parallel group study of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe major depressive disorder without mania (DSM-III 296.2 or 296.3).

Subjects

The protocol called for the random assignment to either paroxetine or placebo of 72 subjects who completed the placebo washout. Inclusion criteria were the same

as for PAR 02-001 and specified a DSM-III diagnosis of depression, age of at least 18 years, a HAM-D score of at least 18 on the first 17 items and a Raskin score of at least 8 and greater than the Covi score. As in PAR 02-001 mania or a fall in HAM-D score of 20% or more between screening and Day 1 were grounds for exclusion. Other exclusionary criteria were identical to PAR 02-001.

Design

Subjects were screened 4-14 days before administration of active drug or placebo and assessed at baseline and 1, 2, 3, 4 and 6 weeks after treatment began. There was a minimum of 14 days of placebo washout for patients who had recently received a MAOI, a minimum 7 days of placebo washout for patients who had recently received psychotropic medication and a 4 day minimum placebo washout for those patients who had not received a psychotropic medication.

Paroxetine dosage was 10-50 mg/d in increments of 10mg taken in the morning. Patients on paroxetine received 20 mg during the first week, 10-30mg/d during the second week and 10-50 mg/d for the next 4 weeks. The only permitted concomitant medication was chloral hydrate for insomnia for a maximum of four consecutive evenings during the interval between the screening examination and Day 7.

The HAMD total was the primary outcome variable. Secondary efficacy variables were the HAM-D retardation factor, (MADRS, SCL-56, CGI, PGE, Raskin depression scale score and Covi Anxiety scale score.

Results

The Intent to Treat Sample was 56% male with a mean age of 36 years. With the exception of marital status (p=.02) the groups did not differ in their demographic characteristics, psychiatric histories or diagnoses. The numbers of paroxetine and placebo patients remaining in the study at 4 weeks was 78% and 77%. 67% of paroxetine patients and 63% of placebo patients completed 6 weeks of treatment.

Mean daily dose in the Intent to Treat sample was 28.5 mg and the mean endpoint dose was 34.7 mg. Average duration in the study was 35.6 days for the paroxetine group and 33.4 days for the placebo patients (p=.48). Average HAM-D scores at baseline were 25.0 for the paroxetine patients and 24.9 for those on placebo (p=.91). Compliance was 102% in the paroxetine group and 104% in the placebo group. (Compliance greater than 100% indicates that subjects took more tablets than the number prescribed.) The change from baseline results (LOCF) for the Intent to Treat and All Efficacy samples at Week 6 were:

02-002

	INTENT TO TREAT				
	Paroxetine		Placebo		
Variable	n	mean (S.E.)	n	mean (S.E.)	p-value
HAM-D Total	36	-10.94 (1.44)	34	-5.77 (1.48)	0.015
HAM-D Depressed Mood Item	36	-1.19 ---	34	-0.50 ---	0.007
HAM-D Retardation Factor	36	-2.83 (0.43)	34	-1.44 (0.44)	0.027
Raskin Total	36	-2.69 (0.42)	34	-1.41 (0.43)	0.035
Severity of Illness	36	-1.06 (0.17)	34	-0.47 (0.18)	0.022
Global Improvement	36	2.58 (0.19)	34	3.38 (0.20)	0.006
Patient's Global Evaluation	36	-0.92 (0.23)	34	-0.38 (0.24)	0.114
SCL Depression Factor	36	-6.94 (1.22)	34	-2.65 (1.25)	0.017
	36	-10.08 (1.63)	34	-5.29 (1.68)	0.044
Covi Anxiety Scale	36	-2.20 (0.37)	34	-0.68 (0.40)	0.008

	EVALUABLE (ALL EFFICACY) PATIENTS				
	Paroxetine		Placebo		
Variable	n	mean (s.e.)	n	mean (s.e.)	p-value
HAM-D Total	32	-11.44 (1.49)	26	-5.50 (1.65)	0.010
HAM-D Depressed Mood Item	32	-1.25 ---	26	-0.38 ---	0.007
HAM-D Retardation Factor	32	-3.00 (0.47)	26	-1.38 (0.52)	0.025
Raskin Total	32	-2.94 (0.43)	26	-1.38 (0.47)	0.018
CGI Severity of Illness	32	-1.13 (0.18)	26	-0.46 (0.20)	0.018
CGI Global Improvement	32	2.50 (0.20)	26	3.46 (0.23)	0.003
Patient's Global Evaluation	32	- 1.00 (0.23)	26	-0.19 (0.25)	0.020
SCL Depression Factor	32	-7.50 (1.26)	26	-1.73 (1.40)	0.004
MADRS	32	-10.72 (1.67)	26	-4.62 (1.85)	0.018
Covi Anxiety Scale	32	-2.00 (0.28)	26	-0.42 (0.31)	0.001

In the Intent to Treat sample, the LOCF analysis of HAM-D total and retardation factors did not achieve significance until week 6 and the visit wise analysis was not significant .1<p<.05 for these variables at endpoint. The HAM-D depressed mood item showed a significant paroxetine effect from week 3 onward by LOCF analysis. Visit wise data was not presented for this variable.

The week 6 SCL depression factor, Raskin, MADRS, CGI Severity and CGI Global Improvement scores which showed significant paroxetine effects by LOCF analysis, did not show a significant effect when visit wise data was analyzed. In each instance of discrepant results on the LOCF and visit-wise analyses the effect size was of equal or near equal magnitude in both analyses, but the standard errors were larger in the smaller visit-wise sample.

At week 4, on both LOCF and visit wise analyses, paroxetine showed significant superiority over placebo on the SCL depression factor, the Patient's Global Evaluation, the CGI Severity and the CGI Global Improvement, but not on the Raskin or the MADRS where the paroxetine advantage did not achieve significance. 15 of 36 (42%) paroxetine patients and 9 of 26 placebo patients (26%) showed a 50% or greater improvement (p=.21).

The sponsor presented LOCF but not visit-wise data for the evaluable patients who did not take any concomitant psychoactive medications . The week 4 results were the same as in the Intent to Treat sample with the exception of the MADRS which showed a significant paroxetine effect among the evaluable patients.

ANCOVA (same covariates as PAR 02-001) performed on the evaluable sample with HAM-D total as the dependent variable showed an interaction of treatment with sex, current condition and episode characterization. In each case the interaction resulted from lack of parallelism, but the lines did not cross and there was a clear treatment effect for paroxetine in each subgroup.

Comment

The consistent week 6 results in both the Intent to Treat and Evaluable samples which showed significant paroxetine superiority over placebo allow this trial to be characterized as a "win". This study had less statistical power than PAR-02-001 which accounts for the discrepancies between the LOCF and visit-wise analyses and the absence of a significant drug effect at week 4 on some of the variables.

Since the daily dose of paroxetine was not fixed, the sponsor reported dosing information. Using the observed cases in the intent-to-treat population, the mean daily dose at week 6 was 36.0 mg/day; the efficacy population used an average of 35.0 mg/day at week 6. In both populations, daily dose steadily increased from baseline to week 6.

Reviewer's Comments

Paroxetine was superior to placebo with respect to the Ham-D Depressed Mood Item in LOCF and OC analyses at 4 and 6 weeks after baseline. On no other outcome was paroxetine consistently better than placebo across all analyses. In fact, on the Ham-D Total paroxetine showed a statistically significantly greater reduction than placebo only in the 6 week LOCF analysis. Furthermore, at both 6 weeks and 4 weeks, reductions in Ham-D Total were statistically significantly lower for paroxetine in the LOCF analyses but were statistically insignificant in the OC analyses. The discrepant results for the Ham-D Total, and for other outcomes, render this trial inconclusive.

PAR 02-003, Ward Smith, Principal Investigator

Study Characteristics

Trial PAR 02-003 employed the same design and variables as PAR 02-002 and PAR 02-001. The target sample size was 72 patients and 77 patients were enrolled.

Sponsor's Statistical Methods

The methods used in this trial were the same as those employed in trials PAR 02-001 and PAR 02-002.

Sponsor's Results

Table 02-003.01 displays the 6 week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. Paroxetine patients showed greater, but statistically insignificant, improvement on all measures in the LOCF analysis. But in the OC analysis, paroxetine displayed less or equal (on Patient's Global Evaluation) improvement as compared to placebo. In the OC analysis of CGI Severity, improvement on placebo was statistically significantly greater than improvement on paroxetine ($p=0.027$). In essence, the LOCF results indicated paroxetine could be better than placebo while the OC results indicated placebo could be better than paroxetine.

PAR 02-003; Ward Smith, Principal Investigator

This was a 6 week, single site, double-blind, placebo controlled, randomized, parallel group study of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe major depressive disorder without mania (DSM-III 296.2 or 296.3).

Subjects

The protocol called for the random assignment to either paroxetine or placebo of 72 subjects who completed a placebo washout. Inclusion criteria were the same as for PAR 02-001 and specified a DSM-III diagnosis of depression, age of at least 18 years, a HAM-D score of at least 18 on the first 17 items and a Raskin score of at least 8 and greater than the Covi score. As in PAR 02-001 mania or a fall in HAM-D score of 20% or more between screening and Day 1 were grounds for exclusion. Other exclusionary criteria were identical to PAR 02-001.

Design

The trial methodology was identical to that of PAR 02-002.

Results

77 patients were enrolled in the study, but 11 (6 paroxetine, 5 placebo) patients were unevaluable because they failed to meet entry criteria or because they were not evaluated during the double blind phase. No patient received a proscribed psychoactive drug during the trial. This group of 66 patients is labeled the "All Efficacy" group.

This sample had a mean age of 45 years and was composed of equal numbers of men and women. Mean daily dose was 33.8 mg and mean endpoint dose was 43.0 mg. Mean duration in the study was 34.8 days for paroxetine patients and 30.6 days for those on placebo (p=.13). Mean baseline HAM-D scores were 28.6 in the paroxetine sample and 28.9 in the placebo group (p=.80). Compliance was 97% for paroxetine patients and 100% for placebo patients. The placebo patients were more likely (p=.01) to have a family member who committed suicide or who was hospitalized for a psychiatric illness (.01).

The number of subjects remaining (%) in the study at each timepoint were:

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	33	33 (100)	32 (97)	30 (91)	28 (85)	21 (64)
Placebo	33	33 (100)	32 (97)	29 (88)	23 (70)	14 (42)

12 paroxetine and 19 placebo patients discontinued. The discrepancy resulted primarily from 16 placebo patients but only 8 paroxetine patients dropping out for lack of efficacy. The large numbers of dropouts requires efficacy to be assessed primarily at 4 weeks.

The change from baseline results at 4 weeks were:

EVALUABLE (ALL EFFICACY) PATIENTS; LAST OBSERVATION CARRIED FORWARD 02-003

Variable	Paroxetine n	Paroxetine mean (s.e.)	Placebo n	Placebo mean (s.e.)	p-value
HAM-D Total	33	-9.73 (1.78)	33	-7.15 (1.78)	0.311
HAM-D Depressed Mood Item	33	-1.06 ---	33	-0.55 ---	0.073
HAM-D Retardation Factor	33	-2.67 (0.53)	33	-1.91 (0.53)	0.319
Raskin Total	33	-2.82 (0.55)	33	-1.85 (0.55)	0.214
CGI Severity of Illness	33	-1.06 (0.24)	33	-0.67 (0.24)	0.253
CGI Global Improvement	33	2.94 (0.28)	33	3.55 (0.28)	0.127
Patient's Global Evaluation	33	-0.73 (0.27)	33	-0.30 (0.27)	0.273
SCL Depression Factor	33	-6.45 (1.52)	33	-3.85 (1.52)	0.230
MADRS	33	-9.24 (1.93)	33	-7.26 (1.93)	0.470
Covi Anxiety Scale	33	-0.67 (0.36)	33	-0.88 (0.36)	0.681

The results at 6 weeks showed a similar absence of significant differences on all variables. Visit-wise data was not provided. Results from the larger Intent to Treat group which contained patients who did not meet entry criteria or who did not have post baseline efficacy data was entirely consistent with the above table at both 4 and 6 weeks. At 4 weeks 36% (12/33) of paroxetine patients and 27% of placebo patients (9/33) showed a 50% improvement in their HAM-D total scores (LOCF; p=.60). At 6 weeks the proportions were 45% (15/33) for paroxetine and 24% (8/33) for placebo (LOCF; p=.12).

There was a significant interaction between treatment and the duration of the present episode. Among patients whose current episode lasted 1-6 months, the mean improvement on the HAM-D at endpoint was 8.00 points for paroxetine and 10.73 points for placebo. Among patients whose current episode lasted longer than 6 months the average paroxetine improvement was 14.60 compared to 5.39 for placebo.

Comment

Although paroxetine patients improved more than placebo patients on this trial, none of the differences were significant. The dose and duration of paroxetine and treatment, level of compliance and the baseline HAM-D scores were similar to almost identical trials in the PAR 02 series which showed statistical superiority for paroxetine over placebo.

PAR 02-004; Ari Kiev, Principal Investigator

This was a 6 week, single site, double-blind, placebo controlled, randomized, parallel group study of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe major depressive disorder without mania (DSM-III 296.2 or 296.3).

Subjects

The protocol called for the random assignment of 72 depressed patients whose characteristics were identical to the other PAR 02 series trials.

Design

The trial methodology was identical to PAR 02-002.

Since the daily dose of paroxetine was not fixed, the sponsor reported dosing information. Using the observed cases in the intent-to-treat population, the mean daily dose at week 6 was 36.0 mg/day; the efficacy population used an average of 35.0 mg/day at week 6. In both populations, daily dose steadily increased from baseline to week 6.

Reviewer's Comments

Paroxetine was superior to placebo with respect to the Ham-D Depressed Mood Item in LOCF and OC analyses at 4 and 6 weeks after baseline. On no other outcome was paroxetine consistently better than placebo across all analyses. In fact, on the Ham-D Total paroxetine showed a statistically significantly greater reduction than placebo only in the 6 week LOCF analysis. Furthermore, at both 6 weeks and 4 weeks, reductions in Ham-D Total were statistically significantly lower for paroxetine in the LOCF analyses but were statistically insignificant in the OC analyses. The discrepant results for the Ham-D Total, and for other outcomes, render this trial inconclusive.

PAR 02-003, Ward Smith, Principal Investigator

Study Characteristics

Trial PAR 02-003 employed the same design and variables as PAR 02-002 and PAR 02-001. The target sample size was 72 patients and 77 patients were enrolled.

Sponsor's Statistical Methods

The methods used in this trial were the same as those employed in trials PAR 02-001 and PAR 02-002.

Sponsor's Results

Table 02-003.01 displays the 6 week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. Paroxetine patients showed greater, but statistically insignificant, improvement on all measures in the LOCF analysis. But in the OC analysis, paroxetine displayed less or equal (on Patient's Global Evaluation) improvement as compared to placebo. In the OC analysis of CGI Severity, improvement on placebo was statistically significantly greater than improvement on paroxetine (p=0.027). In essence, the LOCF results indicated paroxetine could be better than placebo while the OC results indicated placebo could be better than paroxetine.

Table 02-003.01. Mean Change from Baseline to Six Weeks
PAR 02-003, Ward Smith, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-10.08	1.65	39	-7.95	1.70	37	0.371
HamD Dep.	-1.05	NR	39	-0.73	NR	37	0.250
CGI Sev.	-1.10	0.24	39	-0.89	0.25	37	0.543
CGI G.I.	2.92	0.27	39	3.35	0.28	37	0.271
Pat. G.E.	-0.62	0.26	39	-0.35	0.26	37	0.475

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep.	Paroxetine			Placebo			
Var.	Mean	SE	N	Mean	SE	N	p-value
HamD Tot.	-14.27	1.70	26	-16.88	2.17	16	0.350
HamD Dep.	-1.50	0.23	26	-1.63	0.30	16	0.737
CGI Sev.	-1.58	0.25	26	-2.50	0.32	16	0.027
CGI G.I.	2.12	0.23	26	1.75	0.29	16	0.335
Pat. G.E.	-1.27	0.27	26	-1.25	0.35	16	0.966

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

Because only 43 percent of the placebo patients were still in the trial at week 6, the week 4 results were examined. Greater than seventy percent of patients in both treatment groups were left in the trial at week 4. The results at week 4 were generally in the direction favoring paroxetine, but none of the differences was statistically significant.

Since the daily dose of paroxetine was not fixed, the sponsor reported dosing information. Using the observed cases in the intent-to-treat population, the mean daily dose at week 6 was 44.4 mg/day; the efficacy population used an average of 43.8 mg/day at week 6. Among both populations, the daily dose continually increased from baseline to week 6.

Reviewer's Comments

This trial provided no statistical evidence that paroxetine was superior to placebo with regard to the primary and secondary efficacy measures examined.

EVALUABLE (ALL EFFICACY) PATIENTS; LAST OBSERVATION CARRIED FORWARD

Variable	Paroxetine n	Paroxetine mean (s.e.)	Placebo n	Placebo mean (s.e.)	p-value
HAM-D Total	33	-9.73 (1.78)	33	-7.15 (1.7[illegible])	0.311
HAM-D Depressed Mood Item	33	-1.06 ---	33	-0.55 [illegible]	0.073
HAM-D Retardation Factor	33	-2.67 (0.53)	33	-1.91 [illegible].53)	0.319
Raskin Total	33	-2.82 (0.55)	33	-1.[illegible] (0.55)	0.21[illegible]
CGI Severity of Illness	33	-1.06 (0.24)	33	-[illegible].67 (0.24)	0.253
CGI Global Improvement	33	2.94 (0.28)	33	[illegible].55 (0.28)	0.127
Patient's Global Evaluation	33	-0.73 (0.27)	33	-0.30 (0.27)	0.273
SCL Depression Factor	33	-6.45 (1.52)	[illegible]	-3.85 (1.52)	0.230
MADRS	33	-[illegible].24 (1.93)	33	-7.26 (1.93)	0.470
Covi Anxiety Scale	33	-0.67 (0.36)	33	-0.88 (0.36)	0.681

The results at 6 weeks showed a similar absence of significant differences on all variables. Visit-wise data was not provided. Results from the larger Intent to Treat group which contained patients who did not meet entry criteria or who did not have post baseline efficacy data was entirely consistent with the above table at both 4 and 6 weeks. At 4 weeks [illegible]% (12/33) of paroxetine patients and 27% of placebo patients (9/33) showed a 50% improvement in their HAM-D total scores (LOCF; p=.60). At 6 weeks the proportions were 45% (15/33) for paroxetine and 24% (8/33) for placebo (LOCF; p=.12).

There was a significant interaction between treatment and the duration of the present episode. Among patients whose current episode lasted 1-6 months, the mean improvement on the HAM-D at endpoint was 8.00 points for paroxetine and 10.73 points for placebo. Among patients whose current episode lasted longer than 6 months the average paroxetine improvement was 14.60 compared to 5.39 for placebo.

Comment

Although paroxetine patients improved more than placebo patients on this trial, none of the differences were significant. The dose and duration of paroxetine and treatment, level of compliance and the baseline HAM-D scores were similar to almost identical trials in the PAR 02 series which showed statistical superiority for paroxetine over placebo.

PAR 02-004; Ari Kiev, Principal Investigator

This was a 6 week, single site, double-blind, placebo controlled, randomized, parallel group study of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe major depressive disorder without mania (DSM-III 296.2 or 296.3).

Subjects

The protocol called for the random assignment of 72 depressed patients whose characteristics were identical to the other PAR 02 series trials.

Design

The trial methodology was identical to PAR 02-002.

52-004

Results

81 patients were enrolled 3 of whom were not evaluated during the double blind phase. 8 patients randomized to paroxetine and 4 patients randomized to placebo were excluded from the "All Efficacy" analysis. The Intent to Treat sample was 53% male with the mean ages of 35.6 years in the paroxetine group and 41.2 years in the placebo group (p=.11). There were no significant between group differences on any demographic, historical or diagnostic variable. Baseline HAM-D total scores were 28.9 in the paroxetine patients and 27.3 in the placebo group (p=.06).

Mean daily dose of paroxetine was 30.1 mg and mean endpoint dose was 37.1 mg. Mean duration in the trial was 36.4 days for paroxetine patients and 32.5 days for depressed patients on placebo (p=.17). Compliance was 96-97% in each group.

The number of subjects remaining (%) in the study at each timepoint were:

	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	38	38 (100)	38 (100)	33 (87)	32 (84)	22 (58)
Placebo	40	40 (100)	37 (93)	36 (90)	26 (65)	20 (50)

16 paroxetine and 20 placebo patients discontinued. The between group difference in dropouts resulted from 3 paroxetine and 8 placebo patients who discontinued for lack of efficacy. The high proportion of dropouts focuses efficacy assessment on the 4 week evaluation. The change from baseline results (LOCF) for the Intent to Treat and All Efficacy samples at Week 4 were:

INTENT TO TREAT

Variable	Paroxetine n	Paroxetine mean (S.E.)	Placebo n	Placebo mean (S.E.)	p-value
HAM-D Total	36	-12.17 (1.11)	38	-7.16 (1.08)	0.002
HAM-D Depressed Mood Item	36	-1.33 ---	38	-0.76 ---	0.008
HAM-D Retardation Factor	36	-3.00 (0.38)	38	-1.82 (0.37)	0.027
✓Raskin Total	36	-4.50 (0.39)	38	-2.53 (0.38)	0.001
CGI Severity of Illness	36	-1.42 (0.16)	38	-0.68 (0.16)	0.002
CGI Global Improvement	36	2.42 (0.21)	38	3.05 (0.21)	0.037
Patient's Global Evaluation	36	-0.94 (0.20)	38	-0.46 (0.20)	0.093
SCL Depression Factor	36	-8.02 (1.13)	38	-2.85 (1.10)	0.002
✓MADRS	36	-11.92 (1.34)	38	-6.24 (1.31)	0.003
Covi Anxiety Scale	36	-2.17 (0.32)	38	-1.45 (0.31)	0.107

EVALUABLE (ALL EFFICACY) PATIENTS

Variable	Paroxetine n	Paroxetine mean (s.e.)	Placebo n	Placebo mean (s.e.)	p-value
HAM-D Total	34	-12.32 (1.18)	32	-6.66 (1.22)	0.001
HAM-D Depressed Mood Item	34	-1.35 ---	32	-0.72 ---	0.008
HAM-D Retardation Factor	34	-3.03 (0.40)	32	-1.69 (0.42)	0.024
✓Raskin Total	34	-4.62 (0.41)	32	-2.47 (0.42)	<0.001
CGI Severity of Illness	34	-1.41 (0.17)	32	-0.66 (0.17)	0.003
CGI Global Improvement	34	2.35 (0.22)	32	3.16 (0.22)	0.012
Patient's Global Evaluation	34	-0.97 (0.21)	32	-0.41 (0.22)	0.076
SCL Depression Factor	34	-8.10 (1.22)	32	-2.79 (1.26)	0.004
✓MADRS	34	-12.15 (1.39)	32	-5.91 (1.44)	0.003
Covi Anxiety Scale	34	-2.26 (0.33)	32	-1.41 (0.34)	0.072

In the Intent to Treat sample the week 6 LOCF data was entirely consistent with the tabulated week 4 data with the exception of the Patient's Global Evaluation which was significant. The visitwise data at week 4 showed a significant paroxetine effect on the HAM-D total, (Raskin, MADRS, SCL and CGI) severity. The visit wise data at week 6 showed non-significant differences favoring paroxetine for all variables. The disparity between the LOCF and visitwise data at week 6 resulted from larger variances and greater mean improvement from baseline in the placebo group compared to week 4.

In the All Efficacy data set the week 6 LOCF data showed a significant paroxetine effect for all the outcome variables. Visit-wise data was not provided.

The proportions of patients who improved by 50% on the HAMD total were:

	ALL EFFICACY				INTENT TO TREAT			
	Week 4		Week 6		Week 4		Week 6	
Paroxetine	16/34	47%	19/34	56%	16/36	44%	20/37	54%
Placebo	7/32	22%	8/32	25%	8/38	21%	9/38	24%
p		.04		.01		.05		.01

ANCOVA performed on the All Efficacy data did not reveal any significant baseline by treatment interactions.

Comment

In this study paroxetine showed significantly greater efficacy than placebo after 4 and 6 weeks of treatment in last observation carried forward analyses performed on both data sets. Efficacy was consistent over all rating scales. Visitwise analysis on both data sets confirmed paroxetine's efficacy at week 4, but not at week 6 when greater variance and placebo response rendered the paroxetine advantage statistically insignificant.

PAR 03 SERIES

The PAR 03 series comprises six trials with identical protocols which compare paroxetine to imipramine and placebo. The basic protocol design will be described followed by the results at each center.

These studies were six week, single center, randomized, parallel group, imipramine (65-275mg/d) and placebo controlled trials of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe depression without mania (DSM-III 296.2 or 296.3).

Subjects

The inclusion criteria were:

1) DSM-III (296.2 or 296.3) diagnosis of moderate to moderately severe depression,
2) minimum age of 18 years,
3) a screen and baseline HAM-D score of at least 18 on the first 17 items,
4) the score on the 21 item scale could not decrease by more than 20% between the screen and baseline visits,
5) Raskin Depression Scale score at baseline of at least 8 which was also higher than the score on the Covi Anxiety Scale.

PAR 02-004, Ari Kiev, Principal Investigator

Study Characteristics

Trial PAR 02-004 employed the same design and variables as PAR 02-003, PAR 02-002 and PAR 02-001. The target sample size was 72 patients and 81 patients were enrolled.

Sponsor's Statistical Methods

The methods used in this trial were the same as those employed in trials PAR 02-001, PAR 02-002 and PAR 02-003.

Sponsor's Results

Table 02-004.01 displays the six week results for the primary and secondary efficacy variables according to the LOCF and OC analyses of the intent-to-treat population. In the LOCF analyses, subjects receiving paroxetine showed statistically significantly greater improvement than placebo patients on all measures. In the OC analyses, subjects receiving paroxetine showed greater improvement than placebo patients on all measures, but none of the differences between treatments was statistically significant.

Less than 70 percent of placebo patients remained in the trial at week 6. Table 02-004.02 displays the 4 week results. In both the LOCF and OC 4 week analyses, paroxetine showed superior improvement over placebo on the Ham-D Total, Ham-D Depressed Mood Item and CGI Severity. On CGI Severity, paroxetine was superior to placebo according to the LOCF analysis but showed a marginally ($p=0.066$) statistically significant greater improvement than placebo according to the OC analysis. Paroxetine did not differ from placebo, according to both the LOCF and OC analyses, on the Patient's Global Evaluation.

Since the daily dose of paroxetine was not fixed, the sponsor reported dosing information. The observed cases in the intent-to-treat and efficacy populations reported the same mean daily dose at week 6 -- 39.3 mg/day. In the efficacy population, the daily dose steadily increased from baseline to week 6. The mean daily dose increased from week 1 to week 4 and remained about the same at week 6.

Table 02-004.01. Mean Change from Baseline to Six Weeks
PAR 02-004, Ari Kiev, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep. Var.	Paroxetine Mean	SE	N	Placebo Mean	SE	N	p-value
HamD Tot.	-12.65	1.18	37	-7.61	1.16	38	0.003
HamD Dep.	-1.35	NR	37	-0.79	NR	38	0.009
CGI Sev.	-1.46	0.18	37	-0.74	0.18	38	0.006
CGI G.I.	2.30	0.23	37	3.13	0.22	38	0.011
Pat. G.E.	-1.06	0.20	36	-0.40	0.21	35	0.028

Table 02-004.01. Mean Change from Baseline to Six Weeks
PAR 02-004, Ari Kiev, Principal Investigator
(continued)

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep. Var.	Paroxetine Mean	SE	N	Placebo Mean	SE	N	p-value
HamD Tot.	-13.08	1.37	24	-10.25	1.51	20	0.172
HamD Dep.	-1.38	0.19	24	-1.05	0.20	20	0.239
CGI Sev.	-1.54	0.23	24	-1.05	0.26	20	0.163
CGI G.I.	2.17	0.24	24	2.65	0.27	20	0.188
Pat. G.E.	-1.22	0.24	23	-0.65	0.28	17	0.135

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

Table 02-004.02. Mean Change from Baseline to Four Weeks
PAR 02-004, Ari Kiev, Principal Investigator

Sponsor's LOCF Analysis -- Intent-to-Treat Population

Dep. Var.	Paroxetine Mean	SE	N	Placebo Mean	SE	N	p-value
HamD Tot.	-12.17	1.11	36	-7.16	1.08	38	0.002
HamD Dep.	-1.33	NR	36	-0.76	NR	38	0.008
CGI Sev.	-1.42	0.16	36	-0.68	0.16	38	0.002
CGI G.I.	2.42	0.21	36	3.05	0.21	38	0.037
Pat. G.E.	-0.94	0.20	35	-0.46	0.20	35	0.093

Sponsor's Observed Cases Analysis -- Intent-to-Treat Population

Dep. Var.	Paroxetine Mean	SE	N	Placebo Mean	SE	N	p-value
HamD Tot.	-13.15	1.08	33	-8.33	1.19	27	0.004
HamD Dep.	-1.42	0.15	33	-0.85	0.17	27	0.017
CGI Sev.	-1.58	0.17	33	-0.89	0.18	27	0.007
CGI G.I.	2.21	0.19	33	2.74	0.21	27	0.066
Pat. G.E.	-1.13	0.19	32	-0.67	0.22	24	0.127

Note: p-values for HamD Dep. from Model IV; all others from Model II or, if appropriate, Model III.

Stim 1 Fluoxetine (see p2.)

Reviewer's Comments

Trial PAR 02-004 provided adequate statistical evidence that paroxetine was superior to placebo after 4 weeks of treatment.

All five trials used a target sample size of 72 patients for a single center and most enrolled a few less than 72. Only trial PAR 02-004 enrolled more than 72 patients in a single center; it was

the only one with results that consistently demonstrated paroxetine's superiority to placebo. Although its week 6 OC results were statistically insignificant (probably because less than 70 percent of placebo patients remained at week 6) its week 4 results were consistent across analyses. These findings indicated that the sponsor may have underanticipated the dropout rate for the 6 week period.

At week 4 there were 33 paroxetine and 27 placebo patients remaining in the trial. There was a considerable drop at week 6. Nine of the 33 paroxetine patients (27 percent) remaining at week 4 dropped out; 7 of the 27 (26 percent) placebo patients remaining at week 4 dropped out. Up until week 6 the dropout rate for each treatment group was not unusual. The sponsor offered no explanation for the sudden drastic dropoff at week 6. Demographic and clinical characteristics for the patients that left the trial between week 4 and week 6 should be provided by the sponsor in an attempt to explain why the dropout rate suddenly increased.

Reviewer's Conclusions (Which May Be Conveyed To The Sponsor)

Trial PAR 01-001 and the four trials in series PAR 02 were very similar in their design and in the measurements they employed but not in their results. Trials PAR 01-001 and PAR 02-003 failed to demonstrate that paroxetine was superior to placebo. Trial PAR 02-001 provided strong evidence of paroxetine's efficacy when analyzed as a single center trial; that strength was lost in the multicenter analysis. The sponsor provided no explanation for why the subcenter effects were so strong. The results of trial PAR 02-002 were generally favorable to paroxetine but were inconclusive; a statistically significant treatment difference for Ham-D Total was not found in every analysis. Only PAR 02-004 clearly demonstrated paroxetine's superiority to placebo on Ham-D Total, Ham-D Depressed Mood Item, and CGI Severity at week 4. At week 6, PAR 02-004 lost its power due to a sudden increase in the dropout rate.

All five trials used a target sample size of 72 patients for a single center and most enrolled a few less than 72. Only trial PAR 02-004 enrolled more than 72 patients in a single center; it was the only one with results that consistently demonstrated paroxetine's superiority to placebo. Although its week 6 OC results were statistically insignificant (probably because less than 70 percent of placebo patients remained at week), its week 4 results were consistent across analyses. These findings indicated that the sponsor may have underanticipated the dropout rate for the 6 week period.

S. Edward Nevius

for Kenneth R. Petronis, M.S., M.P.H.
Mathematical Statistician

Concur: Dr. Nevius [See Group Leader's Comments on following page.]

Dr. Dubey 9-11-92

PAR 03-001 Investigator Feighner
(conducted May, 1985 to July, 1986)

Sponsor's Results

A total of 118 patients were followed in this study; 40 paroxetine-treated, 38 placebo-treated and 40 imipramine-treated patients. The treatment groups did not differ significantly at baseline with regard to demographics or the efficacy variables. At baseline, approximately 80% of the patients were rated as moderately ill, 15% as markedly ill and the remainder as mildly or borderline mentally ill. Sixty-two percent of the patients were female and 97% were white. The mean age of the patients was approximately 44 years. Eighty-five percent of the patients had previous psychiatric treatment; 1/4 of those patients had been hospitalized for psychiatric treatment for 24 hours or more.

Patient disposition by week on study is shown in the table below. By Week 6 about half of the patients have dropped out of the study. Imipramine-treated patients dropped from the study at a higher rate than the patients in the other groups primarily due to adverse events (see Table 2); all of the 11 imipramine patients who dropped during the first week of study experienced a treatment-related adverse event. Patients in the placebo group dropped from the study primarily due to lack of efficacy while those in the paroxetine group dropped primarily due to an adverse experience.

Table 1. Study 03-001 Patients on Study

WEEK	PAROXETINE	PLACEBO	IMIPRAMINE
1	✓ 40 (100%)	✓ 38 (100%)	40 (100%)
2	35 (88%)	35 (92%)	29 (73%)
3	34 (85%)	32 (84%)	28 (70%)
4	30 (75%)	27 (71%)	21 (53%)
6	✓ 23 (58%)	✓ 20 (53%)	16 (40%)

Table 2. Study 03-001 Reasons for Dropouts

Reason for Dropout	PAROXETINE	PLACEBO	IMIPRAMINE
Lack of efficacy	3 (8%)	10 (26%)	2 (5%)
Lack of efficacy combined with a drug-related adverse experience	6 (15%)	3 (8%)	9 (23%)
Drug-related adverse experience	6 (15%)	0 (0%)	12 (30%)
Other	2 (5%)	5 (13%)	1 (3%)

The sponsor's results for the ITT sample are given in the following sections with tables for each of the efficacy variables. Last-observation-carried-forward (LOCF) results for the 118 patients and observed cases (OC) results based on the numbers in Table 1 are presented for both Weeks 4 and 6. (The results of nonparametric analyses using Model V matched the results of the parametric analyses presented here.)

HAM-D Total

Paroxetine treatment was significantly better than placebo as measured by the HAM-D total at each timepoint from Week 2 to Week 6 for both LOCF and OC analyses. The results for Weeks 4 and 6 are given in Table 3. For imipramine, only the OC analyses produced significant treatment differences compared to placebo beginning at Week 3; the Week 6 LOCF imipramine-placebo comparison was borderline significant with a p-value of .06.

The sponsor's analysis of covariance using 12 different covariates showed no modification of the response due to any single covariate.

Table 3. Sponsor's HAM-D Total Results
ITT Sample of Study 03-001

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	24.9 (0.4)	24.8 (0.4)	24.8 (0.4)	.98
Week 4				
LOCF	-9.8 (1.1)	-5.1 (1.1)	-7.2 (1.1)	.002
OC	-12.2 (1.2)	-6.1 (1.2)	-11.6 (1.3)	<.001
Week 6				
LOCF	✓-10.8 (1.1)	✓-4.7 (1.2)	-7.7 (1.1)	<.001
OC	✓-15.7 (1.2)	✓-7.0 (1.3)	-13.1 (1.4)	<.001

HAM-D Depressed Mood Item

At baseline, the mean response for depressed mood was approximately 3 for all groups (a score of 3 corresponds to a response of "frequent weeping" on this item). Paroxetine-treated patients showed a significantly larger decrease from baseline than the placebo patients at every timepoint from Week 2 to 6. The results in Table 4 show that the LOCF results are consistent with the observed cases results at Week 4 and Week 6. Imipramine results were similar to paroxetine; for the OC analysis, imipramine was significantly different from placebo from Week 2 to Week 6 while for the LOCF analysis the treatment difference is first significant at Week 3.

Table 4. Sponsor's HAM-D Depressed Mood Item Results
ITT Sample of Study 03-001

	PAROXETINE Mean (SE)[1]	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	2.93	2.95	3.03	.20
Week 4				
LOCF	-1.1	-0.4	-1.0	.001
OC	-1.4 (0.2)	-0.5 (0.2)	-1.5 (0.2)	<.001
Week 6				
LOCF	✓ -1.1	✓ -0.3	-1.0	<.001
OC	✓ -1.7 (0.2)	✓-0.6 (0.2)	-1.6 (0.2)	<.001

[1] The sponsor did not include standard errors with the reporting of the means for the LOCF analysis of this variable.

Clinical Global Impression - Severity of Illness

The mean baseline score for CGI severity of illness for all groups was approximately 4 which corresponds to a response of "moderately ill". Both the paroxetine group and the imipramine group showed a mean decrease of about 1 after 4 weeks and 6 weeks of therapy; these changes were statistically significantly different from the placebo response. No pairwise comparisons were significant before Week 4.

Table 5. Sponsor's CGI Severity of Illness Results
ITT Sample of Study 03-001

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	4.1 (0.1)	4.1 (0.1)	4.2 (0.1)	.43
Week 4				
LOCF	-0.8 (0.1)	-0.2 (0.1)	-0.7 (0.1)	.003
OC	-1.1 (0.2)	-0.3 (0.2)	-1.1 (0.2)	.001
Week 6				
LOCF	✓ -0.9 (0.2)	✓-0.3 (0.2)	-0.7 (0.2)	.005
OC	✓ -1.4 (0.2)	✓-0.6 (0.2)	-1.3 (0.2)	.004

Clinical Global Impression - Global Improvement

Paroxetine-treated patients showed improvement superior to placebo at every timepoint for both the LOCF and OC analyses. More improvement was consistently seen for the paroxetine group than the imipramine group with the difference statistically significant for the Week 4 LOCF analysis ($p = .032$). Imipramine beat placebo at Weeks 4 and 6 LOCF and Weeks 3, 4 and 6 OC. After 6 weeks of therapy, about 2/3's of the paroxetine-treated and imipramine-treated patients were considered by the physician to be improved compared to about 1/3 of the placebo-treated patients.

Table 6. Sponsor's CGI Global Improvement Results
ITT Sample of Study 03-001

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Week 4				
LOCF	2.7 (0.2)	3.7 (0.2)	3.2 (0.2)	<.001
OC	2.4 (0.1)	3.5 (0.1)	2.4 (0.2)	<.001
Week 6				
LOCF	2.7 (0.2)	3.7 (0.2)	3.2 (0.2)	<.001
OC	2.0 (0.2)	3.2 (0.2)	2.2 (0.2)	<.001

In the Intent to Treat sample the week 6 LOCF data was entirely consistent with the tabulated week 4 data with the exception of the Patient's Global Evaluation which was significant. The visitwise data at week 4 showed a significant paroxetine effect on the HAM-D total,(Raskin, MADRS, SCL and CGI) severity. The visit wise data at week 6 showed non-significant differences favoring paroxetine for all variables. The disparity between the LOCF and visitwise data at week 6 resulted from larger variances and greater mean improvement from baseline in the placebo group compared to week 4.

In the All Efficacy data set the week 6 LOCF data showed a significant paroxetine effect for all the outcome variables. Visit-wise data was not provided.

The proportions of patients who improved by 50% on the HAMD total were:

	ALL EFFICACY				INTENT TO TREAT			
	Week 4		Week 6		Week 4		Week 6	
Paroxetine	16/34	47%	19/34	56%	16/36	44%	20/37	54%
Placebo	7/32	22%	8/32	25%	8/38	21%	9/38	24%
p				.01		.05		.01

ANCOVA performed on the All Efficacy data did not reveal any significant baseline by treatment interactions.

Comment

In this study paroxetine showed significantly greater efficacy than placebo after 4 and 6 weeks of treatment in last observation carried forward analyses performed on both data sets. Efficacy was consistent over all rating scales. Visitwise analysis on both data sets confirmed paroxetine's efficacy at week 4, but not at week 6 when greater variance and placebo response rendered the paroxetine advantage statistically insignificant.

PAR 03 SERIES

The PAR 03 series comprises six trials with identical protocols which compare paroxetine to imipramine and placebo. The basic protocol design will be described followed by the results at each center.

These studies were six week, single center, randomized, parallel group, imipramine (65-275mg/d) and placebo controlled trials of paroxetine 10-50 mg/d in outpatients with moderate to moderately severe depression without mania (DSM-III 296.2 or 296.3).

Subjects

The inclusion criteria were:

1) DSM-III (296.2 or 296.3) diagnosis of moderate to moderately severe depression,
2) minimum age of 18 years,
3) a screen and baseline HAM-D score of at least 18 on the first 17 items,
4) the score on the 21 item scale could not decrease by more than 20% between the screen and baseline visits,
5) Raskin Depression Scale score at baseline of at least 8 which was also higher than the score on the Covi Anxiety Scale.

Exclusion criteria were:
1) unstabilized renal, hepatic, cardiovascular, respiratory or endocrine disease,
2) history of seizures, glaucoma or urinary retention,
3) psychiatric diagnosis of schizophrenia, atypical depression or anxiety as the primary diagnosis,
4) diagnosis of manic depressive illness or adjustment disorder,
5) patients requiring concomitant therapy with psychoactive drugs,
6) patients known to have abused alcohol within the past six months,
7) a history of ECT within the preceding three months,
8) use of an investigational drug within the preceding 30 days,
9) use of a MAOI within 14 days or use of a psychotropic within the preceding 7 days,
10) patients with a clinically significant abnormal lab value at screen examination,
11) patients who were serious suicidal risks,
12) lactating or pregnant women (wcbp were required to have a negative pregnancy test) and women not practicing a medically acceptable form of contraception,
13) hypertensive patients treated with reserpine, guanethidine, clonidine or methyldopa,
14) patients with a known allergy to imipramine.

Design

A single blind placebo washout followed the screening examination. This phase lasted a minimum of 4 days for patients not previously on psychotropic medication, a minimum of 7 days for those who had received psychotropic medication and a minimum of 14 days for patients who received a MAOI before enrollment in the study.

Patients took medication twice a day from containers marked "morning" and "evening". The paroxetine morning capsules contained 10 mg and the evening capsules did not contain active drug. The imipramine morning tablets contained 15 mg and the evening tablets contained 50 mg. The protocol contained detailed instructions for raising and lowering the dose at each weekly visit. The central rule was that starting from the second dose adjustment, each change of dose consisted of an increase or decrease of one capsule in both the morning and the evening. This defines increments of 10 mg/week for paroxetine and 65 mg/week for imipramine. Paroxetine patients received 20 mg/d and imipramine patients received 80 mg/d during the first week of active treatment. The allowable dose ranges were 10-50 mg/d for paroxetine and 65-275 mg/d for imipramine.

The protocol prohibited the use of any psychotropic medication which could mask or interfere with the actions of paroxetine or imipramine. The only exception was chloral hydrate which was permitted in doses of 500 mg to be taken for insomnia for a maximum of four consecutive nights between screening and day 7.

Patients were evaluated at screening and days 0, 7, 14, 21, 28 and 42. The efficacy variables were the same as those of most of the trials in the PAR 02 series and consisted of the HAM-D, (MADRS) Symptom Check List, CGI, Patient's Global Evaluation (PGE), (Raskin Depression Scale and Covi Anxiety Scale. As in the PAR 02 series, the HAM-D total score at six weeks was the primary efficacy variable. Secondary variables were the HAM-D retardation factor, (Raskin total score, CGI Severity of Illness, CGI Global Improvement and Patient's Global Evaluation.

As in the FAR 02 series the sponsor defined a subset of the Intent to Treat population called the All Efficacy group which deleted from the data set those patients who did not receive 4 days of double blind treatment, who did not meet the selection criteria, whose baseline data was invalidated and those visits which followed within 3 days the ingestion of a prescription or OTC medication with a potential CNS effect. The classes of proscribed drugs were beta blockers. H_2 blockers, anticholinergics, antihistamines, narcotics, psychotropics, centrally acting analgesics or muscle relaxants and sympathomimetics. Although the sponsor focused on the All Efficacy analysis, greater weight will be given to the Intent To Treat analysis.

ANCOVA was performed on the All Efficacy data set with HAM-D total at endpoint as the dependent variable and sex, age, marital status, current condition, onset of present episode, duration of present episode, precipitating external event, episode characterization, previous psychiatric treatment, socioeconomic status and patient head of household as covariates.

PAR 03-001; John Feighner, Principal Investigator

120 patients were enrolled. 2 patients randomized to placebo were not evaluated in the double blind phase. 20 additional patients (4 paroxetine, 7 placebo and 9 imipramine) were excluded from the All Efficacy group. The Intent to Treat patients had the following characteristics:

	Paroxetine N=40	Placebo N=38	Imipramine N=40	p
Mean age	42.4	43.6	47.2	0.13
% male	45	37.5	30	0.40
Baseline HAM-D (SE)	24.9 (0.38)	24.8 (0.39)	24.8 (0.38)	0.98
Mean Daily Capsules (SE)	4.3 (0.2)	5.4 (0.2)	3.9 (0.2)	<.01*
Mean Daily Dose (mg)	26.1	---	110.4	---
Mean Endpoint Dose	30.3	---	125.4	---
# Days in Study (SE)	32.6 (2.2)	31.9 (2.2)	27.0 (2.2)	>.05@
Overall Compliance (%)	100	96	98	

@ Superscripted character signifies "for all 3 between group comparisons".
* For placebo vs. paroxetine and placebo vs. imipramine

With one exception there were no significant between group differences (ANOVA <.05) on any of 42 demographic, historical or diagnostic variables. 3 family members of placebo probands but no family members of the active medication patients had histories of drug abuse.

The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	40	40 (100%)	35 (88%)	34 (85%)	30 (75%)	23 (58%)
Placebo	38	38 (100%)	35 (92%)	32 (84%)	27 (71%)	20 (53%)
Imipramine	40	40 (100%)	29 (73%)	28 (70%)	21 (53%)	16 (40%)

66% of all patients remained in the study after 4 weeks including more than 70% of the paroxetine and placebo patients, but only 50% of the entire sample completed the trial. Accordingly efficacy will be assessed primarily at 4 weeks.

21 of the 24 imipramine dropouts and 12 of 17 paroxetine dropouts discontinued because of an adverse event possibly combined with lack of efficacy. All 11 imipramine discontinuations in the first week were associated with an ADR.

The changes from baseline at 4 weeks in the Intent to Treat group were: 03-001

INTENT TO TREAT- week 4- LOCF

Variable	1-Paroxetine n	mean (S.E.)	2-Placebo n	mean (S.E.)	3-Imipramine n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	39	-9.82 (1.06)	37	-5.08 (1.09)	40	-7.22 (1.05)	<.01	.08
HAM Depressed Mood	39	-1.13 ---	37	-0.43 ---	40	-0.95 ---	<.01	.37
HAM Retardation	39	-2.97 (0.39)	37	-1.70 (0.40)	40	-2.63 (0.39)	.03	.52
Raskin Total	39	-2.54 (0.34)	37	-1.27 (0.35)	40	-2.38 (0.34)	<.01	.73
CGI Severity	39	-0.79 (0.14)	37	-0.19 (0.14)	40	-0.65 (0.14)	<.01	.46
CGI Improvement	39	2.74 (0.16)	37	3.70 (0.16)	40	3.22 (0.16)	<.01	.03
PGE	39	-0.78 (0.24)	36	-0.86 (0.25)	38	-0.82 (0.24)	.82	.92
SCL Depression	39	-2.60 (1.14)	36	-3.52 (1.19)	38	-5.01 (1.16)	.58	.14
MADRS	39	-11.38 (1.47)	37	-4.11 (1.51)	40	-7.63 (1.45)	<.01	.07
Covi Anxiety Scale	39	-1.15 (0.29)	37	-0.46 (0.30)	40	-0.82 (0.29)	.10	.43

Paroxetine-placebo comparisons by Visitwise analysis at week 4 and LOCF analysis at week 6 gave an almost identical pattern of significant results. The only discrepancy was a significant paroxetine advantage over placebo on the Covi at week 6. Paroxetine-placebo comparisons in the All Efficacy data set yielded an identical pattern of paroxetine efficacy. Paroxetine-imipramine comparisons were consistently non-significant with the exception of an imipramine advantage on the SCL on the visit-wise analysis in the Intent To Treat sample and at week 4 in the All Efficacy sample.

In the Intent To Treat sample the proportions of patients who improved by 50% or more in their HAM-D scores (LOCF) were:

	Week 4		Week 6	
Paroxetine	15/39	38%	20/39	51%
Placebo	5/37	14%	4/37	11%
Imipramine	11/40	28%	11/40	28%
p value paroxetine vs. placebo	0.019		<.001	
p value paroxetine vs. imipramine	0.344		0.039	

Analysis of covariance revealed only one significant ($p<.10$) treatment by covariate interaction which was present for the duration of present episode variable which is dichotomized into durations less than and greater than 6 months. The significant interaction arose from clinical deterioration in two imipramine patients whose episode lasted longer than 6 months.

Comment

This study shows a consistent superiority of paroxetine over placebo on almost all of the key outcome variable in both data sets, at various timepoints and by LOCF and visit-wise analyses. Paroxetine demonstrated efficacy despite the low (relative to other trials) doses administered. The SCL depression factor scores were exceptional insofar as the placebo patients actually showed a greater improvement on this measure than the paroxetine patients. This result was

anomalous not only relative to the other outcome measures in this study, but also compared to SCL depression factor scores in other studies. Despite the SCL depression score result, this study is a "win" for paroxetine.

PAR 03-002; Jay Cohn, Principal Investigator

120 patients were enrolled and included in the Intent to Treat analysis. 18 patients (5 paroxetine, 4 placebo, 9 imipramine) were excluded from the All Efficacy analysis. 11 of these 18 patients were excluded for use of a confounding CNS-active medication. The Intent to Treat patients had the following characteristics:

	Paroxetine N=40	Placebo N=40	Imipramine N=40	
Mean age	42.4	42.5	42.3	.70
% male	35	55	37.5	0.18
Baseline HAM-D (SE)	24.9 (.65)	25.6 (.65)	24.4 (.65)	0.45
Mean Daily Capsules (SE)	5.2 (0.2)	5.0 (0.2)	4.9 (0.2)	>.05@
Mean Daily Dose (mg)	30.9	---	140.9	---
Mean Endpoint Dose	37.0	---	168.5	---
# Days in Study (SE)	33.5 (2.2)	28.9 (2.2)	30.1 (.2)	>.05@
Overall Compliance (%)	97	95	92	

@ Superscripted character signifies "for all 3 between group comparisons".

There were no significant between group differences (ANOVA <.05) for any demographic, historical or diagnostic variable. However, a substantial number of patients, particularly those randomized to placebo, failed to complete the study.

		Number of Patients Remaining in Study				
Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	40	40 (100%)	38 (95%)	3 (83%)	27 (68%)	21 (53%)
Placebo	40	40 (100%)	37 (93%)	2 (80%)	22 (55%)	14 (35%)
Imipramine	40	40 (100%)	33 (83%	31 (78%)	25 (63%)	21 (53%)

Given the high and disproportionately distributed number of dropouts, efficacy can only be evaluated at 4 weeks, but even at 4 weeks fewer than 70% of the patients remained in any group. The changes from baseline at 4 weeks in the Intent to Treat and All Efficacy groups were:

	INTENT TO TREAT- Week 4- LOCF							
	1-Paroxetine		2-Placebo		3-Imipramine			
Variable	n	mean (S.E.)	n	mean (S.E.)	n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	40	-8.00 (1.09)	40	-6.22 (1.09)	37	-7.81 (1.13)	.25	.90
HAM Depressed Mo	40	-0.87 ---	40	-0.67 ---	37	-1.03 ---	.32	.47
HAM Retardation	40	-2.2 (0.34)	40	-1.38 (0.34)	37	-2.65 (0.35)	.08	.39
Raskin Total	40	-2.88 (0.33)	40	-1.45 (0.33)	37	-2.46 (0.34)	.003	.39
CGI Severity	40	-0.90 (0.18)	40	-0.70 (0.18)	37	-1.16 (0.18)	.42	.30
CGI Improvement	40	2.50 (0.19)	40	3.08 (0.19)	37	2.32 (0.19)	.04	.52
PGE	40	-0.80 (0.21)	38	-0.34 (0.22)	37	-0.70 (0.22)	.14	.75
SCL Depression	40	-4.47 (1.05)	39	-1.28 (1.06)	37	-5.11 (1.09)	.04	.67
MADRS	40	-8.68 (1.25)	40	-5.80 (1.25)	37	-9.49 (1.30)	.10	.65
Covi Anxiety Scale	40	-1.48 (0.24)	40	-0.82 (0.24)	37	-0.97 (0.25)	.054	.66

anomalous not only relative to th[redacted] compared to SCL depr[redacted] scores in other studies. Despite the SCL depress[redacted], this study is a "win" for paroxetine.

PAR 03-002; Jay Cohn, Principal Investigator

120 patients were enrolled and included in the Intent to Treat analysis. 18 patients (5 paroxetine, 4 placebo, 9 imipramine) were excluded from the All Efficacy analysis. 11 of these 18 patients were excluded for use of a confounding CNS-active medication. The Intent to Treat patients had the following characteristics:

	Paroxetine N=40	Placebo N=40	Imipramine N=40	p
Mean age	42.4	42.5	42.3	0.70
% male	35	55	37.5	0.18
Baseline HAM-D (SE)	24.9 (.65)	25.6 (.65)	24.4 (.65)	0.45
Mean Daily Capsules (SE)	5.2 (0.2)	5.0 (0.2)	4.9 (0.2)	>.05@
Mean Daily Dose (mg)	30.9	---	140.9	---
Mean Endpoint Dose	37.0	---	168.5	---
# Days in Study (SE)	33.5 (2.2)	28.9 (2.2)	30.1 (2.2)	>.05@
Overall Compliance (%)	97	95	92	

@ Superscripted character signifies "for all 3 between group comparisons".

There were no significant between group differences (ANOVA <.05) for any demographic, historical or diagnostic variable. However, a substantial number of patients, particularly those randomized to placebo, failed to complete the study.

		Number of Patients Remaining in Study				
Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	40	40 (100%)	38 (95%)	33 (83%)	27 (68%)	21 (53%)
Placebo	40	40 (100%)	37 (93%)	32 (80%)	22 (55%)	14 (35%)
Imipramine	40	40 (100%)	33 (83%)	31 (78%)	25 (63%)	21 (53%)

Given the high and disproportionately distributed number of dropouts, efficacy can only be evaluated at 4 weeks, but even at 4 weeks fewer than 70% of the patients remained in any group. The changes from baseline at 4 weeks in the Intent to Treat and All Efficacy groups were:

INTENT TO TREAT- Week 4- LOCF

	1-Paroxetine		2-Placebo		3-Imipramine			
Variable	n	mean (S.E.)	n	mean (S.E.)	n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	40	-8.00 (1.09)	40	-6.22 (1.09)	37	-7.81 (1.13)	.25	.90
HAM Depressed Mood	40	-0.87 ---	40	-0.67 ---	37	-1.03 ---	.32	.47
HAM Retardation	40	-2.2 (0.34)	40	-1.38 (0.34)	37	-2.65 (0.35)	.08	.39
Raskin Total	40	-2.88 (0.33)	40	-1.45 (0.33)	37	-2.46 (0.34)	.003	.39
CGI Severity	40	-0.90 (0.18)	40	-0.70 (0.18)	37	-1.16 (0.18)	.42	.30
CGI Improvement	40	2.50 (0.19)	40	3.08 (0.19)	37	2.32 (0.19)	.04	.52
PGE	40	-0.80 (0.21)	38	-0.34 (0.22)	37	-0.70 (0.22)	.14	.75
SCL Depression	40	-4.47 (1.05)	39	-1.28 (1.06)	37	-5.11 (1.09)	.04	.67
MADRS	40	-8.68 (1.25)	40	-5.80 (1.25)	37	-9.49 (1.30)	.10	.65
Covi Anxiety Scale	40	-1.48 (0.24)	40	-0.82 (0.24)	37	-0.97 (0.25)	.054	.66

EVALUABLE (ALL EFFICACY) PATIENTS- Week 4 LOCF

Variable	1-Paroxetine n	mean (S.E.)	2-Placebo n	mean (S.E.)	3-Imipramine n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	35	-8.77 (1.11)	36	-5.44 (1.10)	31	-8.65 (1.18)	.04	.93
HAM Depressed Mood	35	-0.94 ---	36	-0.56 ---	31	-1.16 ---	.06	.32
HAM Retardation	35	-2.40 (0.36)	36	-1.17 (0.36)	31	-2.97 (0.38)	.02	.28
Raskin Total	35	-3.06 (0.35)	36	-1.25 (0.35)	31	-2.68 (0.37)	.001	.46
CGI Severity	35	-1.00 (0.19)	36	-0.61 (0.18)	31	-1.32 (0.20)	.13	.23
CGI Improvement	35	2.37 (0.20)	36	3.33 (0.19)	31	2.16 (0.21)	.003	.46
PGE	35	-0.91 (0.23)	35	-0.23 (0.23)	31	-0.77 (0.25)	.04	.68
SCL Depression	35	-4.97 (1.07)	35	-0.43 (1.07)	31	-5.68 (1.13)	.003	.65
MADRS	35	-9.40 (1.28)	36	-4.81 (1.26)	31	-10.97 (1.36)	.001	.46
Covi Anxiety Scale	35	-1.74 (0.25)	36	-0.72 (0.25)	31	-1.06 (0.27)	.004	.07

Among the Intent To Treat sample there were no significant differences between paroxetine and placebo in the visit wise analysis or the 3 week extender data for the primary variable (HAM-D total) or any of the 4 secondary variables (HAM-D depressed mood and retardation factor, CGI severity and SCL depression factor).

The discrepancy between the Intent To Treat and the All Efficacy data derives from the 5 paroxetine and 4 placebo patients excluded. Ham-D total scores are available at week 4 (either by observation or carry forward) on 4 of these paroxetine and three of these placebo patients. (The remaining two patients were non-responders whose only efficacy evaluation was at 6 weeks). The mean change on the HAM-D total for the paroxetine patients -2.75 and the mean change in the placebo group is -13.3. Changes on the depressed mood item and retardation factor were similar. The exclusion of these patients catapults the paroxetine-placebo difference in the All Efficacy sample over the .05 hurdle.

The potentially psychoactive medication taken by these excluded patients were:

Paroxetine		Placebo
Pt.#023	Premarin .625mg/d, Lomotil 650mg/d	Zantac 1 tab/d
Pt.# 084	Actifed 1 tab/d	Aldomet 250 mg/d
Pt.# 096	Chlor-Trimeton 1 tab/d	Tagamet 200 mg/d
Pt.# 107	L-Tryptophan 500mg/d	

With the possible exception of the placebo patient on Aldomet (who did not improve) these medicacions are unlikely to effect the course of a major depression.

In the Intent To Treat sample the proportions of patients who improved by 50% or more in their HAMD scores (LOCF) were:

	Week 3		Week 6	
Paroxetine	8/40	20%	9/40	23%
Placebo	4/40	10%	6/40	15%
Imipramine	9/37	24%	17/37	46%
p value paroxetine vs. placebo		0.348		0.568
p value paroxetine vs. imipramine		0.785		0.034

Comment

The results in the Intent to Treat sample showing lack of efficacy are more persuasive than the results from the All Efficacy sample where paroxetine was superior to placebo. The exclusion of several paroxetine non-responders and placebo responders from the Intent To Treat group led to a significant treatment effect for paroxetine in the All Efficacy sample. This trial therefore does not demonstrate superiority for paroxetine over placebo in the treatment of depression.

There were no significant differences on parametric measures between the paroxetine and imipramine groups in the Intent To Treat analysis. However, significantly more imipramine than paroxetine patients showed a 50% or more improvement on their HAM-D scores. This pattern is the reverse of PAR 03-01 where a trend favored paroxetine over imipramine in the continuous variables and where a significantly greater proportion of paroxetine patients than imipramine patients improved by 50% or more as assessed by the HAMD total score.

PAR 03-003; Joseph Mendels, Principal Investigator

125 patients were randomized. One patient was never evaluated for efficacy leaving 124 patients in the Intent To Treat sample. 111 patients were included in the All Efficacy sample. The Intent to Treat patients had the following characteristics:

	Paroxetine N=41	Placebo N=	Imipramine N=41	p
Mean age	40.8	41.4	39.6	0.77
% male	39	36	56	0.14
Baseline HAM-D (SE)	25.7 (.65)	27.0 (.65)	26.3 (.65)	0.41
Mean Daily Capsules (SE)	4.6 (0.2)	5 (0.2)	4.6 (0.2)	<.01
Mean Daily Dose (mg)	27.8		133.5	---
Mean Endpoint Dose	33.9		167.3	---
# Days in Study (SE)	33.0 (1.9)	34.0 (1.9)	26.3 (1.9)	>.08
Overall Compliance (%)	94	94	93	

@ Superscripted character signifies for all 3 between group comparisons".

With the exception of a higher number of placebo patients who had a family member with a non-psychotic psychiatric disturbance, there were no between group differences on any demographic, historical or demographic variable. The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	41	41 (100%)	37 (90%)	35 (85%)	30 (73%)	23 (56%)
Placebo	42	42 (100%)	41 (98%)	40 (95%)	33 (79%)	22 (52%)
Imipramine		41 (100%)	36 (88%)	32 (78%)	26 (63%)	17 (41%)

72% of randomized patients were still in the study at week 4, but only half remain at week 6. Accordingly the week 4 assessment will be the primary endpoint.

The changes from baseline at 4 weeks were:

Par 03-002 Investigator Cohn
(Conducted April, 1985 to November, 1986)

Sponsor's Results

A total of 120 patients were enrolled in this study; 40 in each treatment group. The groups were balanced at baseline with regard to demographics, psychiatric history and efficacy measurements. At baseline, about 88% of the patients were rated moderately ill while the remaining patients were rated markedly ill on the CGI. Fifty-eight percent of the patients were females and 98% were white. The mean age of the patients was approximately 42. About half of the patients had experienced previous psychiatric treatment; 25% of these patients had been hospitalized for psychiatric treatment for 24 hours or more.

By Week 6, 53% of the drug-treated patients remained on study while only 35% of the placebo patients were still on study (Table 7). Placebo patients primarily discontinued treatment due to lack of efficacy while the drug-treated patients discontinued primarily due to adverse events (Table 8).

Table 7. Study 03-002 Patients on Study

WEEK	PAROXETINE	PLACEBO	IMIPRAMINE
1	40 (100%)	40 (100%)	40 (100%)
2	38 (95%)	37 (93%)	33 (83%)
3	33 (83%)	32 (80%)	31 (78%)
4	27 (68%)	22 (55%)	25 (63%)
6	21 (53%)	14 (35%)	21 (53%)

Table 8. Study 03-002 Reasons for Dropouts

Reason for Dropout	PAROXETINE	PLACEBO	IMIPRAMINE
Lack of efficacy	3 (8%)	20 (50%)	2 (5%)
Lack of efficacy combined with a drug-related adverse experience	7 (18%)	1 (3%)	6 (15%)
Drug-related adverse experience	6 (15%)	3 (8%)	6 (15%)
Other	3 (8%)	0 (0%)	3 (8%)

The sponsor presented LOCF and OC results for the All Efficacy Patients sample of 102 patients and the intent-to-treat sample. The results for the two samples differed appreciably. Whereas positive results in favor of paroxetine over placebo were observed for the All Efficacy Patients sample on several variables, these results did not hold up for the ITT sample (see Dr. Brecher's review for further details).

For the ITT sample, OC analyses at Weeks 3, 4 and 6 of each of the 5 efficacy variables showed no significant differences between paroxetine and placebo at any timepoint (this was also true for the imipramine-placebo comparison). LOCF analyses showed paroxetine to be significantly superior to placebo only at Week 6 for the HAM-D depressed mood item (Table 9 below) and at Weeks 3, 4 and 6 for the CGI clinical improvement score. (Imipramine was significantly different from placebo at Week 6 LOCF for all the main efficacy variables. At Weeks 3 and 4 LOCF, only the CGI scales for

Comment

The results in the Intent to Treat sample showing lack of efficacy are more persuasive than the results from the All Efficacy sample where paroxetine was superior to placebo. The exclusion of several paroxetine non-responders and placebo responders from the Intent To Treat group led to a significant treatment effect for paroxetine in the All Efficacy sample. This trial therefore does not demonstrate superiority for paroxetine over placebo in the treatment of depression.

There were no significant differences on parametric measures between the paroxetine and imipramine groups in the Intent To Treat analysis. However, significantly more imipramine than paroxetine patients showed a 50% or more improvement on their HAM-D scores. This pattern is the reverse of PAR 03-01 where a trend favored paroxetine over imipramine in the continuous variables and where a significantly greater proportion of paroxetine patients than imipramine patients improved by 50% or more as assessed by the HAMD total score.

PAR 03-003; Joseph Mendels, Principal Investigator

125 patients were randomized. One patient was never evaluated for efficacy leaving 124 patients in the Intent To Treat sample. 111 patients were included in the All Efficacy sample. The Intent to Treat patients had the following characteristics:

	Paroxetine N=41	Placebo N=42	Imipramine N=41	p
Mean age	40.8	41.4	39.6	0.77
% male	39	36	56	0.14
Baseline HAM-D (SE)	25.7 (.65)	27.0 (.65)	26.3 (.65)	0.41
Mean Daily Capsules (SE)	4.6 (0.2)	5.7 (0.2)	4.6 (0.2)	<.01
Mean Daily Dose (mg)	27.8	---	133.5	---
Mean Endpoint Dose	33.9	---	167.3	---
# Days in Study (SE)	33.0 (1.9)	34.0 (1.9)	26.3 (1.9)	>.08
Overall Compliance (%)	94	94	93	

@ Superscripted character signifies "for all 3 between group comparisons".

With the exception of a higher number of placebo patients who had a family member with a non-psychotic psychiatric disturbance, there were no between group differences on any demographic, historical or demographic variable. The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	41	41 (100%)	37 (90%)	35 (85%)	30 (73%)	23 (56%)
Placebo	42	42 (100%)	41 (98%)	40 (95%)	33 (79%)	22 (52%)
Imipramine	41	41 (100%)	36 (88%)	32 (78%)	26 (63%)	17 (41%)

72% of the randomized patients were still in the study at week 4, but only half remained at week 6. Accordingly the week 4 assessment will be the primary endpoint.

The changes from baseline at 4 weeks were:

INTENT TO TREAT- Week 4- LOCF 03-003

Variable	1-Paroxetine n	mean (S.E.)	2-Placebo n	mean (S.E.)	3-Imipramine n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	39	-9.26 (1.32)	42	-9.21 (1.27)	41	-7.80 (1.28)	.98	.43
HAM Depressed Mood	39	-0.92 ---	42	-0.98 ---	41	-0.88 ---	.80	.83
HAM Retardation	39	-2.08 (0.42)	42	-2.62 (0.41)	37	-2.05 (0.41)	.36	.96
Raskin Total	39	-2.08 (0.41)	42	-2.43 (0.40)	41	-2.22 (0.40)	.54	.80
CGI Severity	39	-0.90 (0.20)	42	-1.00 (0.19)	41	-0.80 (0.19)	.71	.74
CGI Improvement	39	2.85 (0.21)	42	2.76 (0.20)	40	2.95 (0.21)	.78	.73
PGE	39	-0.56 (0.21)	40	-0.60 (0.21)	38	-0.63 (0.22)	.91	.82
SCL Depression	39	-4.22 (1.21)	42	-5.08 (1.17)	40	-5.45 (1.20)	.61	.47
MADRS	39	-8.03 (1.58)	40	-9.19 (1.52)	37	-7.07 (1.54)	.60	.67
Covi Anxiety Scale	39	-0.92 (0.32)	42	-0.86 (0.31)	41	-0.39 (0.31)	.88	.24

for HAMD Total + Dep

Results at 6 weeks by LOCF and at 4 weeks by visit-wise analysis were entirely consistent with these tabulated results. Results at 4 and 6 weeks in the All Efficacy group by LOCF were identical. Thus on all 10 measures in each of 5 analyses paroxetine did not show a significant advantage over placebo.

In the Intent To Treat sample the proportions of patients who improved by 50% or more in their HAMD total scores LOCF) were:

	Week 4		Week 6	
Paroxetine	15/39	38%	17/39	44%
Placebo	12/42	29%	14/42	33%
Imipramine	12/41	29%	15/41	37%
p value paroxetine vs. placebo		0.359		0.369
p value paroxetine vs. imipramine		0.480		0.649

Analysis of covariance with HAMD total as the dependent variable revealed significant treatment by covariate interactions for precipitating external event and current treatment status. The significant interactions resulted from isolated cells with 10 or fewer patients who had mean improvements of more than 15 points. Baseline correction for each covariate did not yield any significant between group comparisons on the HAM-D total.

Comment

This study clearly failed to demonstrate any advantage for paroxetine over placebo. The study was characterized by a high proportion (33%) of placebo patients who improved by at least 50% on the HAMD. Similarly the mean improvement in HAMD total scores among placebo patients was a 9.21 points. The results of this trial were atypical insofar as the placebo response at the primary endpoint on several outcome measures, most notably the HAMD depressed mood item and retardation factor, was greater than the response to paroxetine.

PAR 03-004; Ram Shrivastava, Principal Investigator

120 patients were enrolled in th[redacted] whom were included in the Intent to Treat analysis. 107 [redacted] were included in the All Efficacy group. The Intent to [redacted] had the following characteristics:

severity of illness and global improvement showed imipramine superior to placebo.)

The LOCF results of the ITT sample for the HAM-D total and HAM-D depressed mood item, the two most important efficacy variables, are given below (for results of the other variables, see Dr. Brecher's review).

Table 9. Study 03-002 HAM-D LOCF Means - ITT Sample

	HAM-D TOTAL			HAM-D DEPRESSED MOOD ITEM		
WEEK	PAR	PLA	IMP	PAR	PLA	IMP
Baseline	24.9	25.6	24.4	3.0	3.0	2.9
1	-3.4	-3.0	-4.2	-0.3	-0.3	-0.5
2	-5.8	-4.8	-6.7	-0.7	-0.5	-0.8 *
3	-7.3	-5.4	-7.4	-0.9	-0.7	-1.0
4	-8.0	-6.2	-7.8	-0.9	-0.7	-1.0
6	-8.6	-5.6	-9.6 *	-1.1 *	-0.7	-1.2 *

* Results significantly different from placebo, $p < .05$.

It can be seen that the drug-treatment groups show improvement over time but the changes, generally, are not significantly different from the placebo changes.

It should be noted that the sponsor also reanalyzed the All Efficacy Patients sample including patients who had been dropped due to concomitant medication use; the results of this analysis were consistent with the ITT sample results shown above.

Reviewer's Comments

Due to the large number of dropouts after only three weeks of therapy, the OC analyses comparing paroxetine to placebo at Weeks 4 and 6 lack power to detect an important difference. At Week 4, the power to detect a difference of 5 on the HAM-D Total given the observed sample sizes (Table 7) and assuming alpha of .05 and a standard deviation of 6.5. is 74%; at Week 6, the power given the observed sample sizes is 58%. Also a large number of patients drop from the study due to lack of efficacy in all groups (26% of the paroxetine patients, 53% of the placebo patients and 20% of the imipramine patients), so the treatment effects at Weeks 4 and 6 using the LOCF data may underestimate the true effects in each treatment group since one is assuming that dropouts would not have improved had they continued on study. One might expect the drug group effects to be underestimated to a larger extent than the placebo effects (therefore biasing against drug) since, judging from the other studies in this series, the largest changes in response are seen after more than 3 weeks of therapy. The HAM-D total and CGI severity of illness means for paroxetine were about 10% smaller than the means observed in the other studies under the PAR 03 protocol.

One is left then with looking at Week 3 data only. The LOCF and OC results for HAM-D total, HAM-D depression mood item, CGI severity and PGE at Week 3 did not significantly favor paroxetine over placebo; only the treatment difference for CGI global improvement was significant ($p = .013$).

For imipramine, at Week 3, only the CGI for severity and global improvement responses were significantly different from placebo according to the LOCF analyses. As for paroxetine, imipramine was not significantly different from placebo for any OC analysis after 2 weeks.

In conclusion, this study failed to show statistically that paroxetine is superior to placebo for the treatment of depression. Imipramine, also, was not shown to be consistently significantly different from placebo.

Par 03-003 Investigator Mendels
(Conducted May, 1985 to September, 1986)

Sponsor's Results

The sponsor enrolled 124 patients; 41 paroxetine-treated, 42 placebo-treated and 41 imipramine-treated. The treatment groups did not differ at baseline on any demographic or primary efficacy variable. At baseline about 60% of the patients were rated moderately ill; the remainder were rated markedly ill. Fifty-six percent of the patients were female and 92% were white. The mean age of the patients was about 41 years. Approximately 75% of the patients had been treated previously for a psychiatric illness; about 15% of these patients had been hospitalized for 24 hours or more.

The dropout pattern in this study is similar to what was seen for the other studies in the PAR 03 series; more than 70% of the patients completed 4 weeks while only about 50% completed 6 weeks (Table 10). Patients in the placebo group primarily discontinue from the study due to lack of efficacy while patients in the drug-treated groups discontinue primarily due to experiencing an adverse event (Table 11).

Table 10. Study 03-003 Patients on Study

WEEK	PAROXETINE	PLACEBO	IMIPRAMINE
1	✓41 (100%)	✓42 (100%)	41 (100%)
2	37 (90%)	41 (98%)	36 (88%)
3	35 (85%)	40 (95%)	32 (78%)
4	30 (73%)	33 (79%)	26 (63%)
6	✓23 (56%)	✓22 (52%)	17 (41%)

OC

Table 11. Study 03-003 Reasons for Dropouts

Reason for Dropout	PAROXETINE	PLACEBO	IMIPRAMINE
Lack of efficacy	7 (17%)	17 (40%)	4 (10%)
Lack of efficacy combined with a drug-related adverse experience	2 (5%)	2 (5%)	6 (15%)
Drug-related adverse experience	7 (17%)	0 (0%)	13 (32%)
Other	2 (5%)	1 (2%)	1 (2%)

The efficacy results showed no significant differences between paroxetine and placebo for any analyses of the primary efficacy variables. This was also true for the imipramine-placebo comparison. All three treatment groups showed improvement over time as can be seen in the following table of HAM-D Total and HAM-D depressed mood item LOCF results. The magnitude of response for the placebo group was as large as the responses observed for the drug treatment groups; similar results were seen for the other primary efficacy variables as well.

Table 12. Study 03-003 HAM-D LOCF Means - ITT Sample

	HAM-D TOTAL			HAM-D DEPRESSED MOOD ITEM		
WEEK	PAR	PLA	IMP	PAR	PLA	IMP
Baseline	25.7	27.0	26.3	2.8	2.9	2.7
1	-3.9	-3.6	-3.6	-0.6	-0.3	-0.3
2	-7.2	-5.9	-5.8	-0.8	-0.5	-0.7
3	-8.1	-8.7	-6.6	-0.9	-0.9	-0.7
4	-9.3	-9.2	-7.8	-0.9	-1.0	-0.9
6	-9.9	-10.0	-9.0	-1.3	-1.0	-1.0

The OC results for HAM-D total given below show that the patients who remain on study continue to show improvement in all three treatment groups.

	Paroxetine	Placebo	Imipramine
Week 4 OC HAM-D total	-11.7	-10.9	-11.1
Week 6 OC HAM-D total	-14.2	-15.8	-17.3

As for the HAM-D, the CGI results showed improvement on both the severity scale (50% improved) and the global improvement scale (minimally improved at Week 1 to much improved at Week 6) for all three treatment groups.

Reviewer's Comments

The magnitude of the drug responses to both paroxetine and imipramine are consistent with what has been observed in other studies in this submission; the placebo response, however, is larger than what has generally been seen for the PAR-03 series. Therefore the comparisons to placebo were consistently small across all the primary efficacy variables regardless of the dataset used or type of analysis. This trial, then, failed to show paroxetine superior to placebo for the treatment of depression. In addition, this trial also failed to show the active control, imipramine, superior to placebo.

INTENT TO TREAT- Week 4- LOCF

Variable	1-Paroxetine n	mean (S.E.)	2-Placebo n	mean (S.E.)	3-Imipramine n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	39	-9.26 (1.32)	42	-9.21 (1.27)	41	-7.80 (1.2[illegible]	.98	.43
HAM Depressed Mood	39	-0.92 ---	42	-0.98 ---	41	-0.88 [illegible]	.80	.83
HAM Retardation	39	-2.08 (0.42)	42	-2.62 (0.41)	37	-2.05 [illegible]1)	.36	.96
Raskin Total	39	-2.08 (0.41)	42	-2.43 (0.40)	41	-2.22 [illegible].40)	.54	.80
CGI Severity	39	-0.90 (0.20)	42	-1.00 (0.19)	41	-0[illegible] (0.19)	.71	.74
CGI Improvement	39	2.85 (0.21)	42	2.76 (0.20)	40	[illegible]5 (0.21)	.78	.73
PGE	39	-0.56 (0.21)	40	-0.60 (0.21)	38	[illegible].63 (0.22)	.91	.82
SCL Depression	39	-4.22 (1.21)	42	-5.08 (1.17)	[illegible]	5.45 (1.20)	.61	.47
MADRS	39	-8.03 (1.58)	40	-9.19 (1.52)	[illegible]	-7.07 (1.54)	.60	.67
Covi Anxiety Scale	39	-0.92 (0.32)	42	-0.86 (0.31)	[illegible]1	-0.39 (0.31)	.88	.24

Results at 6 weeks by LOCF and at 4 weeks by [illegible]t-wise analysis were entirely consistent with these tabulated results. [illegible]ts at 4 and 6 weeks in the All Efficacy group by LOCF were identical. [illegible] on all 10 measures in each of 5 analyses paroxetine did not show a signif[illegible]nt advantage over placebo.

In the Intent To Treat sample the prop[illegible]ions of patients who improved by 50% or more in their HAMD total scores LOCF [illegible]ere:

	Week 4		Week 6	
Paroxetine	[illegible]5/39	38%	17/39	44%
Placebo	12/42	29%	14/42	33%
Imipramine	12/41	29%	15/41	37%
p value paroxetine vs. pl[illegible]bo	0.359		0.369	
p value paroxetine vs. i[illegible]pramine	0.480		0.649	

Analysis of covaria[illegible] with HAMD total as the dependent variable revealed significant treatme[illegible] by covariate interactions for precipitating external event and current treatm[illegible] status. The significant interactions resulted from isolated cells with 10 or [illegible]wer patients who had mean improvements of more than 15 points. Baseline correl[illegible]on for each covariate did not yield any significant between group comparisons [illegible]the HAM-D total.

Comment

This st[illegible] clearly failed to demonstrate any advantage for paroxetine over placeb[illegible] The study was characterized by a high proportion (33%) of placebo pati[illegible] who improved by at least 50% on the HAMD. Similarly the mean improvement in [illegible]D total scores among placebo patients was a 9.21 points. The results of th[illegible]trial were atypical insofar as the placebo response at the primary endpoint [illegible]several outcome measures, most notably the HAMD depressed mood item and [illegible]tardation factor, was greater than the response to paroxetine.

PAR 03-004: Ram Shrivastava, Principal Investigator

120 patients were enrolled in the trial all of whom were included in the Intent to Treat analysis. 107 patients were included in the All Efficacy group. The Intent to Treat patients had the following characteristics:

	Paroxetine N=40	Placebo N=40	Imipramine N=40	p
Mean age	37.2	34.3	32.1	0.64
% male	63	58	55	0.85
Baseline HAM-D (SE)	27.6 (.62)	27.0 (.62)	26.5 (.52)	0.50
Mean Daily Capsules (SE)	5.4 (0.2)	5.2 (0.2)	5.8 (0.2)	>.05@
Mean Daily Dose (mg)	32.1	---	138.5	---
Mean Endpoint Dose	39.8	---	177.5	---
# Days in Study (SE)	32.4 (2.4)	30.4 (2.4)	24.3 (2.4)	<.02*
Overall Compliance (%)	93	94	89	

@ Superscripted character signifies "for all 3 between group comparisons".
* for paroxetine vs. imipramine comparison

There were no significant ($p<.05$) between group differences on any demographic, historical or diagnostic variable.

The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	40	40 (100%)	31 (78%)	30 (75%)	29 (73%)	26 (65%)
Placebo	40	40 (100%)	35 (88%)	29 (73%)	25 (79%)	18 (45%)
Imipramine	40	40 (100%)	32 (80%)	28 (70%)	19 (48%)	10 (25%)

73% of the sample was still in the trial after 3 weeks, 61% remained after 4 weeks and 45% completed the study. The week 4 assessment is the least biased timepoint for analysis of efficacy because it provides adequately long exposure and adequate numbers of paroxetine and placebo patients.

The changes from baseline at 4 weeks were:

630004

INTENT TO TREAT- Week 4- LOCF

Variable	1-Paroxetine n	1-Paroxetine mean (S.E.)	2-Placebo n	2-Placebo mean (S.E.)	3-Imipramine n	3-Imipramine mean (S.E.)	p 1vs2	p 1vs3
HAM Total	37	-10.35 (1.26)	37	-6.65 (1.26)	40	-5.75 (1.21)	.04	.01
HAM Depressed Mood	37	-1.08 ---	37	-0.62 ---	40	-0.70 ---	.052	.11
HAM Retardation	37	-2.46 (0.42)	37	-1.84 (0.42)	40	-1.67 (0.41)	.30	.19
Raskin Total	37	-2.89 (0.42)	37	-1.65 (0.42)	40	-2.00 (0.40)	.04	.13
CGI Severity	37	-0.84 (0.16)	37	-0.57 (0.16)	40	-0.52 (0.15)	.23	.16
CGI Improvement	37	2.70 (0.20)	37	3.24 (0.20)	40	3.35 (0.19)	.06	.02
PGE	36	-0.89 (0.22)	34	-0.38 (0.23)	40	-0.38 (0.21)	.12	.10
SCL Depression	37	-3.88 (1.10)	36	-0.69 (1.11)	40	-1.58 (1.06)	.04	.13
MADRS	37	-11.46 (1.65)	37	-7.49 (1.65)	40	-7.22 (1.59)	.09	.07
Covi Anxiety Scale	37	-1.65 (0.31)	37	-0.84 (0.31)	40	-0.32 (0.30)	.07	<.01

The results in the Intent to Treat sample are inconsistent. On the primary efficacy variable (HAM-D total) and one (SCL depression factor) of the 4 FDA designated secondary variables paroxetine was significantly superior to placebo. On the remaining three secondary variables (HAM-D retardation factor, HAM-D depressed mood item and CGI severity) the difference was insignificant although the trend favored paroxetine. The depressed mood item was nearly significant at 4 weeks and was significant at 6 weeks ($p<.03$). The SCL which was significant in the above table did not reach significance at week 6 by LOCF or at weeks 4 and 6

by visit-wise analysis. For the HAM-D total and other three secondary the results at week 6 by either LOCF or visit-wise analysis were consi the results in the above table. At 6 weeks the CGI improvement, MADR were all significant on the LOCF.

The results in the All Efficacy sample for all ten variables at both 4 a were, with one minor exception, identical to the those observed in the Treat group.

The proportions of patients who improved by 50% or more in their HAM (LOCF) were:

	Intent to Treat		All Efficacy	
	Week 4	Week 6	Week 4	Wee
Paroxetine	13/37 35%	16/37 43%	13/33 39%	16/
Placebo	7/37 19%	9/37 24%	7/36 19%	9/
Imipramine	6/40 15%	8/40 20%	6/38 16%	8/
p value paroxetin vs. placebo	0.19	0.14	0.11	
p value paroxetine vs. imipramine	0.06	0.05	0.03	

Analysis of covariance with HAM-D total as the dependent variable rev significant (p=.084) age by treatment interaction. Patients older than 4C greater improvement on paroxetine compared to placebo or imipramine than p younger than 40. Baseline correction did not alter the statistical compa

Comment

Patients in this trial were somewhat younger than those who participated at centers. The significant advantage for paroxetine over imipramine on th total and in the proportion of patients who improved by 50% on the HAMD was biased in favor of paroxetine by the substantially greater numbe imipramine dropouts. These patients who discontinued primarily because of ad incidents did not remain in the study for a sufficient duration to benefit the spontaneous improvement which was observed in the placebo group.

The study provides support rather than evidence for paroxetine's superiority placebo. Paroxetine "wins" on the HAM-D, the primary outcome variable and or secondary variable (SCL depression), but on the other three secondary varia paroxetine did not clear the .05 hurdle. Moreover, SCL depression which sh a significant effect at 4 weeks did not show a significant effect at 6 weeks w depressed mood which narrowly missed at 4 weeks was significant at 6 weeks collective results on 10 outcome variables computed in two slightly diffe populations at two different endpoints and by two different methods of anal all indicate that paroxetine has antidepressant potency. The data however do adequately distance this impression from the realm of chance and do not allow study to be unambiguously categorized as a "win".

[redacted]005; Ronald Fieve, Principal Investigator

121 patients [redacted] olled of whom 2 were lost after the baseline visit lea 119 patients in the [redacted] eat sample. The All Efficacy sample include of these patients. The [redacted] patients had the follo characteristics:

Reviewer's Comments

The Week 4 LOCF results for HAM-D total and HAM-D depressed mood item show a significant treatment difference between paroxetine and placebo but the OC results do not. Also, no other primary or secondary variables showed paroxetine to be consistently better than placebo.

To further examine the results at Week 4, Dr. Masahiro Takeuchi (FDA Division of Biometrics, HFD-713) reanalyzed the HAM-D total data using the generalized estimating equation (GEE) approach. This procedure uses all the data available for each patient, not only the data from a single week. The results of this analysis showed paroxetine significantly different from placebo on the HAM-D total ($p < .04$). (Dr. Takeuchi's results will appear in a separate report.)

The imipramine response as seen in Tables 15 and 16 was smaller than the paroxetine response and not different from the placebo response. This lack of a significant treatment effect for imipramine over placebo may be due to the large number of dropouts in that drug group, much larger than was seen in the other studies. That is, the LOCF means for imipramine are probably underestimates of the true treatment effects due to the large number of patients who drop early, before a response is generally expected. This is born out by the fact that the patients in the imipramine group that complete the study show a notably larger treatment effect than placebo on the HAM-D total and on both CGI scores. Therefore, this lack of effect for the active control does not necessarily suggest that the trial was a failed trial incapable of distinguishing paroxetine from placebo.

Due to the lack of positive effects on most of the efficacy variables, this reviewer would not consider this trial as a clear "win" for paroxetine, however, the HAM-D results provide supportive statistical evidence of the benefit of paroxetine in the treatment of depression. Also, it is notable that significantly more patients in the paroxetine group completed the study than in the imipramine group suggesting a better benefit-risk ratio for paroxetine than imipramine.

Par 03-004 Investigator Shrivastava
(Conducted May, 1985 to December, 1986)

Sponsor's Results

One hundred twenty patients were entered in this study; 40 patients were randomized to each of the 3 treatment groups. The treatment groups were comparable at baseline with regard to demographics and primary efficacy measures. At baseline, 79% of the patients were rated moderately ill and 21% markedly ill. About 42% of the patients were female and 89% were white. The mean age of the patients was 34.5 years; 62% of the patients were under the age of 35 years. About 66% of the patients had experienced previous psychiatric treatment; only 9% of those patients had ever been hospitalized for psychiatric treatment for 24 or more hours.

More than 70% of the patients were still on study after 3 weeks of therapy; thereafter appreciably more patients dropped from the placebo group and imipramine group such that at Week 6 less than 50% of the patients remained on study in those two groups (Table 13). Statistically significantly more patients completed the study in the paroxetine group than in the imipramine group, ($p = .001$).

Table 13. Study 03-004 Patients on Study

WEEK	PAROXETINE	PLACEBO	IMIPRAMINE
1	40 (100%)	40 (100%)	40 (100%)
2	31 (78%)	35 (88%)	32 (80%)
3	30 (75%)	29 (73%)	28 (70%)
4	29 (73%)	25 (63%)	19 (48%)
6	26 (65%)	18 (45%)	10 (25%)

The reasons for withdrawal follow a different pattern than what was seen in the other studies under the PAR 003 protocol in that a large percentage of patients fall into the "other" category (Table 14). Of the total number of patients withdrawing due to other reasons, about 2/3's dropped due to reasons unrelated to drug (for example, trauma and respiratory disorder) and about 1/3 for reasons unknown. Also, the percentage of placebo patients dropped due to lack of efficacy is notably smaller than what was observed for other studies in this series; usually more than one-third of the patients drop due lack of efficacy in this group. The imipramine dropout pattern, however, was consistent with what has been seen in other studies with significantly more patients dropping due to adverse events in the imipramine group than the other two treatment groups ($p < .01$).

Table 14. Study 03-004 Reasons for Dropouts

Reason for Dropout	PAROXETINE	PLACEBO	IMIPRAMINE
Lack of efficacy	3 (8%)	6 (15%)	2 (5%)
Lack of efficacy combined with a drug-related adverse experience	1 (3%)	2 (5%)	8 (20%)
Drug-related adverse experience	6 (15%)	4 (10%)	11 (28%)
Other	4 (11%)	10 (26%)	9 (23%)

Due to the small percentage of patients remaining on study by Week 6, only the sponsor's ITT sample results for Weeks 3 and 4 are presented in the following tables. Also, only the HAM-D total and HAM-D depressed mood item results are shown. No statistically significant treatment differences were observed for the CGI global improvement score and the PGE at Weeks 3 and 4; paroxetine was significantly different from placebo on the CGI severity of illness score only at Week 3 for the OC analysis.

The HAM-D total results at Week 4 (Table 15) show paroxetine beats placebo according to the LOCF analysis ($p = .04$) but not according to the OC analysis ($p = .12$). In addition, the placebo response is slightly larger than the imipramine response; this was not seen in the other PAR 03 studies. The results for the completers at Week 6 are more consistent with what was seen for this variable in the other studies; the response for the drug groups was about -15 and for the placebo group -10.2 .

Table 15. Sponsor's HAM-D Total Results
ITT Sample of Study 03-004

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	27.6 (0.6)	27.0 (0.6)	26.5 (0.6)	.49
Week 3				
LOCF	-8.1 (1.1)	-5.6 (1.1)	-5.0 (1.1)	.10
OC	-9.8 (1.3)	-6.4 (1.3)	-6.3 (1.3)	.07
Week 4				
LOCF	-10.4 (1.3)	-6.7 (1.3)	-5.8 (1.2)	.04
OC	✓ -12.4 (1.3)	✓ -9.3 (1.5)	-9.7 (1.7)	.12 ← OC

As for the HAM-D total, the sponsor's ITT results for the HAM-D depressed mood item favor paroxetine over placebo only at Week 4 LOCF (Table 16). The response for the imipramine group is not significantly different from the placebo response.

Table 16. Sponsor's HAM-D Depressed Mood Item Results
ITT Sample of Study 03-004

	PAROXETINE Mean (SE)[1]	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	2.8	2.7	2.9	.24
Week 3				
LOCF	-0.8	-0.6	-0.6	.27
OC	-1.1 (0.2)	-0.7 (0.2)	-0.7 (0.2)	.10
Week 4				
LOCF	-1.1	-0.6	-0.7	.05
OC	✓ -1.3 (0.2)	✓ -0.8 (0.2)	-1.1 (0.3)	.11 ← OC

[1] Standard errors were not provided for the LOCF data.

PAR 03-005 Investigator Fieve
(Conducted July, 1985 to December, 1986)

Sponsor's Results

A total of 119 patients were enrolled in this study; 40 in the paroxetine group, 42 in the placebo group and 37 in the imipramine group. At baseline, 63% of the patients were rated moderately ill on the CGI severity scale; 28% were rated markedly ill and the remaining 9% were rated severely ill on the CGI. The average age of the sample was about 44 years. Thirty-one percent of the patients were female (the lowest percentage in any of the studies); 9.2% of the patients were black (the highest percentage in any of the studies).

The groups were comparable at baseline on demographic and efficacy variables with the exception of one variable; previous psychiatric treatment. The imipramine group had a significantly higher proportion of patients who had been previously treated for psychiatric treatment (86%) compared to the placebo group (60%) or the paroxetine group (70%). More than one third of the imipramine and paroxetine patients had been hospitalized for 24 hours or longer while only about 1/4 of the placebo-treated patients had been previously hospitalized for psychiatric treatment.

A notably higher percentage of patients remained on study for the duration of this 6-week trial compared to any other study conducted under the PAR 03 protocol (Table 17). In addition, unlike the other studies, fewer patients dropped out in the imipramine group than in the other two treatment groups.

Table 17. Study 03-005 Patients on Study

WEEK	PAROXETINE	PLACEBO	IMIPRAMINE
1	40 (100%)	42 (100%)	37 (100%)
2	36 (90%)	41 (98%)	33 (89%)
3	34 (85%)	40 (95%)	32 (86%)
4	31 (79%)	33 (79%)	31 (84%)
6	29 (73%)	31 (74%)	28 (76%)

The placebo patients predominately dropped due to lack of efficacy. The number of patients reporting adverse events in the drug treatment groups was smaller than what was generally reported for the PAR 03 studies; on the average, more than 25% of the imipramine patients and about 15% of the paroxetine patients reported adverse events in the other 5 studies. In the "other" category, exactly half of the patients in each group dropped for non-drug related reasons and the other half dropped for unknown reasons.

Table 18. Study 03-005 Reasons for Dropouts

Reason for Dropout	PAROXETINE	PLACEBO	IMIPRAMINE
Lack of efficacy	1 (3%)	6 (14%)	1 (3%)
Lack of efficacy combined with a drug-related adverse experience	2 (5%)	1 (2%)	3 (8%)
Drug-related adverse experience	2 (5%)	0 (0%)	1 (3%)
Other	6 (16%)	4 (10%)	4 (10%)

by visit-wise analysis. For the HAM-D total and other th[illegible] secondary the results at week 6 by either LOCF or visit-wise analy[illegible] were consi the results in the above table. At 6 weeks the CGI i[illegible]ovement, MADR were all significant on the LOCF.

The results in the All Efficacy sample for all ten [illegible]iables at both 4 a were, with one minor exception, identical to the[illegible]ose observed in the Treat group.

The proportions of patients who improved by [illegible]0% or more in their HAM (LOCF) were:

	Intent to T[illegible]at				All Efficacy			
	Week 4		Week 6		Week 4		Wee	
Paroxetine	13/37	3[illegible]	16/37	43%	13/33	39%	16/	
Placebo	7/37	[illegible]	9/37	24%	7/36	19%	9/	
Imipramine	6/40	[illegible]%	8/40	20%	6/38	16%	8/	
p value paroxetin[illegible] vs. placebo	[illegible]9		0.14		0.11			
p value paroxetine vs. imipramine	[illegible]06		0.05		0.03			

Analysis of covariance with HA[illegible] total as the dependent variable rev significant (p=.084) age by tre[illegible]ent interaction. Patients older than 4[illegible] greater improvement on paroxe[illegible]e compared to placebo or imipramine than p younger than 40. Baseline c[illegible]rrection did not alter the statistical compa

Comment

Patients in this trial w[illegible]e somewhat younger than those who participated at centers. The signifi[illegible]t advantage for paroxetine over imipramine on th total and in the pr[illegible]rtion of patients who improved by 50% on the HAMD was biased in fav[illegible] of paroxetine by the substantially greater numb imipramine dropou[illegible] These patients who discontinued primarily because of ad incidents did no[illegible]remain in the study for a sufficient duration to benefit the spontaneou[illegible]mprovement which was observed in the placebo group.

The study p[illegible]ides support rather than evidence for paroxetine's superiority placebo. [illegible]oxetine "wins" on the HAM-D, the primary outcome variable and or secondary [illegible]ariable (SCL depression), but on the other three secondary varia paroxeti[illegible] did not clear the .05 hurdle. Moreover, SCL depression which sh a signi[illegible]cant effect at 4 weeks did not show a significant effect at 6 weeks w depre[illegible]d mood which narrowly missed at 4 weeks was significant at 6 weeks coll[illegible]tive results on 10 outcome variables computed in two slightly diffe po[illegible]ations at two different endpoints and by two different methods of anal al[illegible]indicate that paroxetine has antidepressant potency. The data however do [illegible]quately distance this impression from the realm of chance and do not allow [illegible]udy to be unambiguously categorized as a "win".

PAR 03-005; Ronald Fieve, Principal Investigator

121 patients were enrolled of whom 2 were lost after the baseline visit lea 119 patients in the Intent to Treat sample. The All Efficacy sample include of these patients. The Intent to Treat patients had the follo characteristics:

	Paroxetine N=40	Placebo N=42	Imipramine N=37	p
Mean age	43.8	44.7	43.1	0.80
% male	58	76	73	0.17
Baseline HAM-D (SE)	26.1 (.82)	26.8 (.80)	27.4 (.85)	0.53
Mean Daily Capsules (SE)	5.3 (0.2)	5.9 (0.2)	5.5 (0.2)	>.05@
Mean Daily Dose (mg)	31.6	---	161.6	---
Mean Endpoint Dose	38.3	---	197.5	---
# Days in Study (SE)	36.0 (1.9)	37.3 (1.9)	36.8 (2.0)	>.05@
Overall Compliance (%)	94	97	110	

@ Superscripted character signifies "for all 3 between group comparisons".

With the exception of previous psychiatric treatment (p=.03) there were no significant (p<.05) between group differences on any demographic, historical or diagnostic variable. 68% of the placebo group had not received any prior psychiatric care. For 43% of paroxetine patients and 16% of imipramine patients this study represented their first exposure to psychiatric treatment.

The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	40	40 (100%)	36 (90%)	34 (85%)	31 (78%)	29 (73%)
Placebo	42	42 (100%)	41 (98%)	40 (95%)	33 (79%)	31 (74%)
Imipramine	37	37 (100%)	33 (89%)	32 (86%)	31 (84%)	28 (76%)

This study, unlike its 4 predecessors in the PAR 03 series, did not have a problem with discontinuations. Efficacy can therefore be assessed at the planned 6 week endpoint. The changes from baseline at 4 weeks were:

INTENT TO TREAT- Week 6- LOCF

	1-Paroxetine		2-Placebo		3-Imipramine			
Variable	n	mean (S.E.)	n	mean (S.E.)	n	mean (S.E.)	p 1vs2	p 1vs3
HAM Total	40	-10.02 (1.56)	42	-4.07 (1.52)	36	-15.56 (1.21)	.007	.016
HAM Depressed Mood	40	-1.32 ---	42	-0.55 ---	36	-1.72 ---	.003	.09
HAM Retardation	40	-3.22 (0.47)	42	-1.29 (0.46)	36	-4.81 (0.50)	.004	.023
Raskin Total	40	-2.80 (0.47)	42	-1.45 (0.46)	36	-4.44 (0.49)	.042	.017
CGI Severity	40	-1.05 (0.19)	42	-0.48 (0.19)	36	-1.78 (0.20)	.035	.011
CGI Improvement	40	2.75 (0.23)	42	3.76 (0.22)	36	2.28 (0.24)	.002	.16
PGE	40	-1.10 (0.23)	42	-0.07 (0.23)	36	-1.64 (0.24)	.002	.11
SCL Depression	40	-6.69 (1.23)	42	-2.71 (1.20)	36	-9.43 (1.30)	.023	.13
MADRS	38	-12.25 (1.83)	42	-4.76 (1.79)	36	-17.47 (1.93)	.004	.052
Covi Anxiety Scale	40	-0.52 (0.26)	42	0.05 (0.25)	36	-0.97 (0.27)	.12	.24

Results at week 6 on the visit-wise analysis for the paroxetine-placebo and paroxetine-imipramine comparisons was similar to the LOCF for all variables except the Raskin and the CGI severity. Results in the All Efficacy group at week 6 by LOCF were, not surprisingly, identical with the results observed in the Intent to Treat sample.

In the Intent To Treat sample the proportions of patients who improved by 50% or more in their HAM-D total scores were:

	Week 6	
Paroxetine	16/40	40%
Placebo	12/42	29%
Imipramine	21/36	58%
p value paroxetine vs. placebo	0.353	
p value paroxetine vs. imipramine	0.011	

Analysis of Covariance with HAM-D total score as the dependent variable disclosed significant ($p<.10$) treatment by covariate interactions for sex, marital status. onset of present episode and current treatment status. After baseline correction the significant advantage of paroxetine over placebo and of imipramine over paroxetine remained unchanged. Comparison of the means of each subgroup for each of the 4 significant covariates revealed that: (means in parenthesis, s.e. in brackets)
males responded much than females to imipramine (-17.72 [1.93] vs. -10.30 [3.06]);
patients who were married responded better to paroxetine than single patients (-12.37 [1.88] vs. -5.50 [2.82]);
patients whose episode was shorter than one month did better on imipramine than those whose episode was longer (-24.00 [3.99] vs. -13.86 [1.81]) and
patients who were not receiving psychiatric treatment at entry did better on placebo than those who were in treatment (-6.50 [1.76] vs. 2.17 [2.79].

Comment
This is the only trial in the PAR 03 series in which more than 70% of patients in all three treatment groups completed 6 weeks of treatment. This study provides evidence for the effectiveness of paroxetine in outpatients with major depression. This result is not surprising. More unusual is the greater improvement with imipramine than with paroxetine, a result which attained or approached significance on nearly all outcome variables and in the proportion of patients who improved by at least 50% in their HAM-D total scores. This may have resulted from the higher doses of imipramine (197.5 mean endpoint dose) given in this trial. The mean endpoint dose of imipramine was at least 20mg/d higher than in any of the other PAR 03 series active control trials.

Par 03-006; Louis Fabre, Principal Investigator

120 patients were randomized 116 of whom had at least one efficacy [illegible]ation. 5 patients had taken a concomitant psychoactive medication leav[illegible] patients in the All Efficacy sample. The Intent to Treat sampl[illegible] the following characteristics:

	Paroxetine N=39	Plac[illegible]=38	Imipramine N=39	p
Mean age	35.7	[illegible]	35.1	0.86
% male	44	[illegible]	33	0.66
Baseline HAM-D (SE)	29.7 (.62)	28.7 (.63)	27.9 (.62)	0.12
Mean Daily Capsules (SE)	4.7 [illegible]	4.7 (0.2)	4.7 (0.2)	>.05@
Mean Daily Dose (mg)	[illegible]	----	134.5	---
Mean Endpoint Dose	[illegible].6	---	164.2	---
# Days in Study ([illegible])	29.6 (2.1)	23.1 (2.1)	28.6 (2.1)	<.05*
Overall Compli[illegible] (%)	95	96	95	

@ Sup[illegible]ipted character signifies "for all 3 between group comparisons".
* [illegible] paroxetine-placebo comparison

The sponsor's efficacy results show paroxetine statistically significantly superior to placebo on each of the 5 primary efficacy variables from Week 3 to Week 6 (the Week 6 results only are given in Table 19). The imipramine response in this trial was larger than the paroxetine response for each of the 5 variables; for HAM-D total and CGI severity of illness, imipramine was statistically significantly better than paroxetine. Also, imipramine was found to be significantly superior to placebo as early as Week 2; a week earlier than paroxetine.

Table 19. Study 03-005 Sponsor's ITT Efficacy Results

Efficacy Variable	Paroxetine Mean (SE)	Placebo Mean (SE)	Imipramine Mean (SE)	p-value PAR vs PLA
HAM-D Total				
Baseline	26.1 (0.8)	26.8 (0.8)	27.4 (0.9)	.53
Week 6 LOCF	-10.0 (1.6)	-4.1 (1.5)	-15.6 (1.6)	.007
Week 6 OC	✓-11.9 (1.8)	✓-5.7 (1.8)	-17.7 (1.9)	.017
HAM-D Depressed Mood Item				
Baseline	3.0	3.0	2.9	.86
Week 6 LOCF	-1.3	-0.6	-1.7	.003
Week 6 OC	✓ -1.4	✓-0.7	-1.9	.02
CGI Severity				
Baseline	4.4 (0.1)	4.5 (0.1)	4.5 (0.1)	.91
Week 6 LOCF	-1.1 (0.2)	-0.5 (0.2)	-1.8 (0.2)	.04
Week 6 OC	✓ -1.2 (0.2)	✓-0.7 (0.2)	-2.1 (0.2)	.12
CGI Global				
Week 6 LOCF	2.8 (0.2)	3.8 (0.2)	2.3 (0.2)	.002
Week 6 OC	2.5 (0.3)	3.5 (0.3)	2.0 (0.3)	.01
PGE				
Baseline	4.0 (0.1)	4.0 (0.1)	3.9 (0.1)	.50
Week 6 LOCF	-1.1 (0.2)	-0.1 (0.2)	-1.6 (0.2)	.002
Week 6 OC	-1.3 (0.3)	-0.4 (0.3)	-1.9 (0.3)	.01

Reviewer's Comments

This study clearly shows, statistically, that paroxetine is effective in the treatment of depression when compared to placebo.

The large, early significant responses to imipramine observed in this study may be due to the larger doses used in this study (see the Dosing section of this review) as noted by Dr. Brecher (HFD-120) in his review. It is possible also, since a higher proportion of imipramine patients had undergone previous psychiatric treatment than the paroxetine and placebo patients, that the imipramine patients may have been more responsive to treatment.

PAR 03-006 Investigator Fabre
(Conducted April, 1985 to July, 1986)

Sponsor's Results

A total of 116 patients were followed in this study; 39 were treated with paroxetine, 38 with placebo and 39 with imipramine. The treatment groups were not significantly different at baseline for any demographic or efficacy variables. At baseline, the CGI severity of illness scores showed 46% of the patients were moderately ill, 50% were markedly ill and 4% were severely ill. Three of the 4 patients rated as severely ill at baseline were in the paroxetine group. The average age of the patients was about 36. Sixty-two percent were female and 88% of the patients were white. About 2/3's of the patients had undergone previous psychiatric treatment; of those patients, 25% had been hospitalized for 24 hours or more.

Compared to the other 5 PAR 03 studies, this study had the fewest total number of patients still on study by Week 6. After only two weeks of therapy, about 30% of the placebo patients discontinued from the study; half of those dropouts discontinued due to lack of efficacy. About 40% of the patients in each of the drug treatment groups completed the study while only 18% of the placebo patients completed the 6 weeks of therapy.

Table 20. Study 03-006 Patients on Study

WEEK	PAROXETINE	PLACEBO	IMIPRAMINE
1	39 (100%)	38 (100%)	39 (100%)
2	35 (90%)	35 (92%)	33 (85%)
3	30 (77%)	24 (63%)	29 (74%)
4	22 (56%)	13 (34%)	20 (51%)
6	16 (41%)	7 (18%)	17 (44%)

Table 21. Study 03-006 Reasons for Dropouts

Reason for Dropout	PAROXETINE	PLACEBO	IMIPRAMINE
Lack of efficacy	8 (21%)	20 (53%)	6 (15%)
Lack of efficacy combined with a drug-related adverse experience	4 (10%)	2 (5%)	4 (10%)
Drug-related adverse experience	6 (15%)	3 (8%)	6 (15%)
Other	5 (13%)	6 (16%)	6 (16%)

Due to the small number of patients completing this study (particularly in the placebo group) only the results for Weeks 3 and 4 are presented (Tables 22 to 25).

The HAM-D total results clearly favor paroxetine over placebo at Weeks 3 and 4 (Table 22) with p-values less than .02 for both the OC and LOCF analyses. The groups were also different at Week 2 and Week 6. The magnitude of the placebo response (LOCF) is notably smaller than the responses observed in the other studies in this series; -3 versus values usually smaller than -5, respectively.

Table 22. Sponsor's HAM-D Total Results
ITT Sample of Study 03-006

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	29.7 (0.6)	28.7 (0.6)	27.9 (0.6)	.12
Week 3				
LOCF	-7.4 (1.1)	-3.1 (1.1)	-6.5 (1.1)	.007
OC	-9.0 (1.3)	-4.2 (1.3)	-8.0 (1.3)	.01
Week 4				
LOCF	-7.9 (1.2)	-3.4 (1.2)	-7.3 (1.2)	.01
OC	-12.4 (1.4)	-6.9 (1.7)	-11.2 (1.4)	.02

As for HAM-D total, the results for HAM-D depressed mood item clearly show paroxetine to be superior to placebo. Again the treatment difference was statistically significant as early as Week 2 and through to Week 6. Imipramine, on the other hand, only beats placebo at Week 3 OC and Week 6 OC.

Table 23. Sponsor's HAM-D Depressed Mood Item Results
ITT Sample of Study 03-006

	PAROXETINE Mean (SE)[1]	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	3.08	3.03	2.82	.16
Week 3				
LOCF	-0.8	-0.4	-0.7	.03
OC	-1.0 (0.2)	-0.5 (0.2)	-1.0 (0.2)	.04
Week 4				
LOCF	-0.9	-0.4	-0.7	.04
OC	-1.4 (0.2)	-1.1 (0.2)	-1.2 (0.2)	.37

[1] The sponsor did not include standard errors with the reporting of the means for the LOCF analysis of this variable.

At baseline, the paroxetine and placebo patients were comparable (p=.19) with both groups rated as markedly ill on the CGI severity of illness scale. The paroxetine and imipramine baselines, however, were significantly different with p=.02. The paroxetine patients showed significant improvement over the placebo patients from Week 2 to Week 6 based on the LOCF and OC analyses. Also, imipramine beat placebo from Week 3 to Week 6.

Table 24. Sponsor's CGI Severity of Illness Results
ITT Sample of Study 03-006

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Baseline	4.7 (0.1)	4.6 (0.1)	4.4 (0.1)	.19
Week 3				
LOCF	-1.0 (0.2)	-0.3 (0.2)	-0.7 (0.2)	.001
OC	-1.2 (0.2)	-0.3 (0.2)	-0.9 (0.2)	.001
Week 4				
LOCF	-1.1 (0.2)	-0.3 (0.2)	-0.9 (0.2)	.001
OC	-1.6 (0.2)	-0.6 (0.2)	-1.3 (0.2)	.004

According to the CGI global improvement score, both drug treatment groups showed steady improvement over the 6 weeks of the study while the placebo group was rated as minimally improved with mean values of about 3 at each timepoint. The paroxetine mean responses ranged from about 3 (minimally improved) at Week 1 to about 1 (very much improved) at Week 6 OC. Paroxetine was statistically significantly different from placebo at Weeks 3, 4 and 6.

Table 25. Sponsor's CGI Global Improvement Results
ITT Sample of Study 03-006

	PAROXETINE Mean (SE)	PLACEBO Mean (SE)	IMIPRAMINE Mean (SE)	P-VALUE PAR vs PLA
Week 3				
LOCF	2.7 (0.2)	3.5 (0.2)	2.9 (0.2)	.008
OC	2.4 (0.2)	3.4 (0.2)	2.5 (0.2)	.002
Week 4				
LOCF	2.7 (0.2)	3.5 (0.2)	2.7 (0.2)	.008
OC	2.0 (0.2)	2.9 (0.3)	2.0 (0.2)	.01

	Week 6	
Paroxetine	16/40	40%
Placebo	12/42	29%
Imipramine	21/36	58%
p value paroxetine vs. placebo	0.353	
p value paroxetine vs. imipramine	0.011	

Analysis of Covariance with HAM-D total score as the dependent variable disclosed significant (p<.10) treatment by covariate interaction for sex, marital status. onset of present episode and current treatment status. After baseline correction the significant advantage of paroxetine over placebo and of imipramine over paroxetine remained unchanged. Comparison of the means of each subgroup for each of the 4 significant covariates revealed that (means in parenthesis, s.e. in brackets)
males responded much than females to imipramine (-17.72 [1.93] vs. -10.30 [3.06]);
patients who were married responded better to paroxetine than single patients (-12.37 [1.88] vs. -5.50 [2.82]);
patients whose episode was shorter than one month did better on imipramine than those whose episode was longer (-14.00 [3.99] vs. -13.86 [1.81]) and
patients who were not receiving psychiatric treatment at entry did better on placebo than those who were in treatment (-6.50 [1.76] vs. 2.17 [2.79].

Comment

This is the only trial in the PAR 03 series in which more than 70% of patients in all three treatment groups completed 6 weeks of treatment. This study provides evidence for the effectiveness of paroxetine in outpatients with major depression. This result is not surprising. More unusual is the greater improvement with imipramine than with paroxetine, a result which attained or approached significance on nearly all outcome variables and in the proportion of patients who improved by at least 50% in their HAM-D total scores. This may have resulted from the higher doses of imipramine (197.5 mean endpoint dose) given in this trial. The mean endpoint dose of imipramine was at least 20mg/d higher than in any of the other PAR 03 series active control trials.

Par 03-006; Louis Fabre, Principal Investigator

120 patients were randomized 116 of whom had at least one efficacy evaluation. 5 patients had taken a concomitant psychoactive medication leaving 111 patients in the All Efficacy sample. The Intent to Treat sample had the following characteristics:

	Paroxetine N=39	Placebo N=38	Imipramine N=39	p
Mean age	35.7	36.4	35.1	0.86
% male	44	37	33	0.66
Baseline HAM-D (SE)	29.7 (.62)	28.7 (.63)	27.9 (.62)	0.12
Mean Daily Capsules (SE)	4.7 (0.2)	4.7 (0.2)	4.7 (0.2)	>.05@
Mean Daily Dose (mg)	28.5	---	134.5	---
Mean Endpoint Dose	34.6	---	164.2	---
# Days in Study (SE)	29.6 (2.1)	23.1 (2.1)	28.6 (2.1)	<.05*
Overall Compliance (%)	95	96	95	

@ Superscripted character signifies "for all 3 between group comparisons".
* For paroxetine-placebo comparison

03-006

There were two significant ($p<.05$) between group differences on demographic, historical or diagnostic variables. The placebo and imipramine groups were both more likely to have a lineal family member with a nonpsychotic psychiatric disturbance than the paroxetine cohort. The paroxetine patients also experienced more unemployment in the preceding three years than imipramine or placebo patients.

The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	39	39 (100%)	35 (90%)	30 (77%)	22 (56%)	16 (41%)
Placebo	38	38 (100%)	35 (92%)	24 (63%)	13 (34%)	7 (18%)
Imipramine	39	39 (100%)	33 (85%)	29 (74%)	20 (51%)	17 (44%)

Only one patient discontinued because of improvement. 34 patients (8 paroxetine, 20 placebo and 6 imipramine) dropped out for lack of efficacy. Another 10 patients (4 paroxetine, 2 placebo and 4 imipramine) dropped out for lack of efficacy combined with an adverse event.

The changes from baseline on the HAM-D total in the Intent to Treat sample were:

LOCF

	Week 2		Week 3		Week 4		Week 6	
	N	Mean (s.e.)	N	Mean (s.e.)	N	Mean (s.e.)	N	Mean (s.e.)
Paroxetine	39	-7.13 (1.06)	39	-7.46 (1.11)	39	-7.85 (1.19)	39	-9.08 (1.29)
Placebo	37	-4.03 (1.09)	37	-3.11 (1.14)	37	-3.38 (1.22)	37	-2.97 (1.32)
Imipramine	39	-5.99 (1.06)	39	-6.49 (1.11)	39	-7.26 (1.19)	39	-7.62 (1.29)
parox. vs. placebo		p=.044		p=.007		p=.01		p=.001
parox. vs. imipramine		p=.30		p=.54		p=.72		p= 42

Visit-wise

	Week 2		Week 3		Week 4		Week 6	
	N	Mean (s.e.)	N	Mean (s.e.)	N	Mean (s.e.)	N	Mean (s.e.)
Paroxetine	33	-8.42 (1.10)	26	-9.04 (1.27)	20	-12.40 (1.38)	17	-15.94 (1.32)
Placebo	34	-4.35 (1.08)	24	-4.17 (1.33)	13	-6.92 (1.71)	7	-3.43 (2.06)
Imipramine	33	-7.00 (1.10)	26	-8.04 (1.27)	20	-11.20 (1.38)	17	-13.88 (1.32)
parox. vs. placebo		p=.010		p=.010		p=.016		p<.001
parox. vs. imipramine		p=.36		p=.58		p=.54		p=.28

An identical pattern of significant results were observed on the HAM-D retardation factor. On the HAM-D depressed mood item, which was only assessed by LOCF, paroxetine was superior to placebo at Weeks 2, 3, 4 and 6 and not significantly different than imipramine at Weeks 3, 4 and 6.

On the SCL depression factor paroxetine was superior to placebo at Weeks 3, 4 and 6 by LOCF, but only beat placebo at Week-3 on the visit wise analysis. A comparison of paroxetine and imipramine did not show a significant treatment effect.

Paroxetine was superior to placebo at Weeks 2, 3, 4 and 6 on the CGI severity scale on both the LOCF and visitwise analyses. Paroxetine-imipramine comparisons were not significant at Weeks 3, 4 and 6.

With one minor exception (Week 2, global improvement. LOCF) paroxetine was superior to placebo on the Raskin, MADRS and CGI global improvement at Weeks 2, 3, 4 and 6 on both the LOCF and visit-wise analyses.

Similar patterns of efficacy were observed in the All Efficacy data set in which only LOCF analyses were performed.

In the Intent To Treat sample the proportions of patients who improved by 50% or more in their HAM-D total scores were:

	Week 6	
Paroxetine	12/39	31%
Placebo	3/37	8%
Imipramine	10/39	26%
p value paroxetine vs. placebo	0.02	
p value paroxetine vs. imipramine	0.80	

Analysis of covariance in the All Efficacy sample did not reveal any significant ($p<.10$) treatment by covariate interactions for any of the 10 variables examined.

Comment

The patients in this trial had a mean HAMD score at baseline of 28.8 is higher than any of the previously reviewed trial. Paroxetine dosages were in the low end of the range observed thus far. These two factors may have contributed to the high dropout rate for lack of efficacy.

Paroxetine showed consistent efficacy over placebo in both the LOCF and visit-wise analyses. The manifestation of a significant treatment effect after only two weeks of treatment is further indication of paroxetine's antidepressant action. The change from baseline in the paroxetine patients were similar to that observed in other trials. Despite the small number of subjects remaining at week 6 in the visit-wise analysis and the limited power of the statistical comparison, paroxetine was able to demonstrate superiority over placebo. Despite the high proportion of dropouts, the study provides evidence for paroxetine's effectiveness as an antidepressant.

PAR 04

This study was a six center, double blind, placebo controlled exten[illegible] PAR 03. It was conducted at the same 6 centers as PAR 03 with t[illegible] 6 principal investigators.

Subjects and Design

Only subjects who were enrolled in PA[illegible]ould participate in the extension. Patients who completed Protocol 0[illegible]d elect to continue on the same drug (or placebo) in Protocol 04 or, i[illegible]y received-active drug in PAR 03, could cross over to the alternate ac[illegible]ug. Patients crossing over from placebo were given paroxetine. Patie[illegible]ctive drug who dropped out of Protocol 03 due to lack of efficacy o[illegible]se experiences could cross over to the alternate active drug in Protoc[illegible]. Following 1 year of treatment under Protocol 04, only paroxe[illegible]treated patients could enter an open-label extension that provided for an [illegible]ional 3 years of paroxetine therapy.

The PGE results showed no statistically significant differences between either paroxetine or imipramine and placebo at any week of the study. The completers data (Week 6 OC) showed "minimal improvement" in the placebo group and "much improvement" in the two drug groups while the LOCF data shows "minimal improvement" in all 3 groups.

Reviewer's Comments

The dropout pattern in this study is similar to the one seen for Study 03-002 in that only a small number of patients in the placebo group completed the study while the number of completers in each of the drug treatment groups was about double that amount. However, unlike Study 03-002, the results from this study are overwhelmingly positive. The 4 primary efficacy variables (HAM-D total, HAM-D depressed mood item, CGI severity of illness and CGI global improvement) show paroxetine superior to placebo for the treatment of depression. The treatment differences were significant from Week 2 to Week 6 and for both the LOCF and OC analyses. (Similar results were seen also for the imipramine-placebo comparison.) Study 03-006 provides strong statistical evidence of the efficacy of paroxetine over placebo for the treatment of depression.

With one minor exception (Week 2, global improvement. LOCF) paroxetine was superior to placebo on the Raskin, MADRS and CGI global improvement at weeks 2, 3, 4 and 6 on both the LOCF and visit-wise analyses.

Similar patterns of efficacy were observed in the All Efficacy data set in which only LOCF analyses were performed.

In the Intent To Treat sample the proportions of patients who improved by 50% or more in their HAM-D total scores were:

	Week 6	
Paroxetine	12/39	31%
Placebo	3/37	8%
Imipramine	10/39	26%
p value paroxetine vs. placebo	0.02	
p value paroxetine vs. imipramine	0.8	

Analysis of covariance in the All Efficacy sample did not reveal any significant ($p<.10$) treatment by covariate interactions for any of the 10 variables examined.

Comment

The patients in this trial had a mean HAMD score at baseline of 28.8 is higher than any of the previously reviewed trial. Paroxetine dosages were in the low end of the range observed thus far. These two factors may have contributed to the high dropout rate for lack of efficacy.

Paroxetine showed consistent efficacy over placebo in both the LOCF and visit-wise analyses. The manifestation of a significant treatment effect after only two weeks of treatment is further indication of paroxetine's antidepressant action. The change from baseline in the paroxetine patients were similar to that observed in other trials. Despite the small number of subjects remaining at week 6 in the visit-wise analysis and the limited power of the statistical comparison, paroxetine was able to demonstrate superiority over placebo. Despite the high proportion of dropouts, the study provides evidence for paroxetine's effectiveness as an antidepressant.

PAR 04

This study was a six center, double blind, placebo controlled extension of PAR 03. It was conducted at the same 6 centers as PAR 03 with the same 6 principal investigators.

Subjects and Design

Only subjects who were enrolled in PAR 03 could participate in the extension. Patients who completed Protocol 03 could elect to continue on the same drug (or placebo) in Protocol 04 or, if they received active drug in PAR 03, could cross over to the alternate active drug. Patients crossing over from placebo were given paroxetine. Patients on active drug who dropped out of Protocol 03 due to lack of efficacy or adverse experiences could cross over to the alternate active drug in Protocol 04. Following 1 year of treatment under Protocol 04, only paroxetine-treated patients could enter an open-label extension that provided for an additional 3 years of paroxetine therapy.

Crossover patients were dosed according to the PAR 03 titration schedule. Patients who continued on the same treatment could have their medication raised or lowered by one pill in both the morning and evening. The capsules were of the same strength as in PAR 03.

The only permitted concomitant psychoactive medication was occasional 500mg chloral hydrate for insomnia.

Patients who did not cross over were treated for another 336 days and were evaluated on day 70 and at 6 week intervals thereafter. Crossover patients were treated for 378 days and were evaluated at the same time points as the patients whose treatment did not change.

The efficacy instruments were the same as in PAR 03.

Results

529 patients were enrolled in PAR 04, 517 of whom comprised the Intent to Treat sample. Mean age of patients who received paroxetine, imipramine or placebo were all 41 years. 44% of paroxetine, 72% of placebo and 49% of imipramine patients were male. Compliance was recorded as close to 100% in all three groups. 503 of the Intent to Treat patients had at least 1 efficacy evaluation. The Intent to Treat sample had the following characteristics:

Treatment (*) Crossover	N (evaluable)	MDD[1]	MED[2]	Days in Study
Parox (Imi)	89	37.0	33.7	113.5
Imi (Parox)	77	191.7	161.7	121.2
Parox (Placebo)	127	---	---	148.8
Continuation				
Parox (Parox)	93	42.4	36.3	188.6
Imi (Imi)	75	200.6	178.0	169.7
Placebo (Placebo)	42	---	---	161.3

* (PAR 03 treatment); 1-Mean Maximum Daily Dose; 2-Mean Endpoint Dose

The number of patients remaining in the study at each timepoint were:

Treatment (*)	Number Enrolled	Number of Patients Completing Interval (%) 6 weeks	3 months	6 months	9 months	1 year
Crossovers						
Paroxetine (Imipramine)	91	52 (57)	34 (37)	23 (25)	14 (15)	13 (14)
Imipramine (Paroxetine)	79	44 (56)	33 (42)	22 (28)	16 (20)	13 (16)
Paroxetine (Placebo)	128	82 (64)	61 (48)	47 (37)	38 (30)	31 (24)
Continuation						
Paroxetine (Paroxetine)	94	82 (87)	67 (71)	50 (53)	34 (36)	26 (28)
Imipramine (Imipramine)	79	58 (73)	49 (62)	39 (49)	27 (34)	18 (23)
Placebo (Placebo)	46	38 (83)	30 (65)	17 (37)	12 (26)	9 (20)
All patients	517	356 (69)	274 (53)	198 (38)	141 (27)	110 (21)

* Treatment in parenthesis is PAR 03 treatment.

This large crossover study has two components. The first is the comparison of non-responders from PAR 03 who switched to either imipramine or paroxetine. The second comparison is for maintenance of improvement in paroxetine, imipramine and placebo responders who continued the treatment they received in PAR 03.

The three groups of patients who remained on their PAR 03 treatment had similar dropout rates. Patients who crossed over to the other active drug discontinued more frequently than patients who did not switch, but the dropout rates for the paroxetine (imipramine) and imipramine (paroxetine) were similar. Data is presented below for the HAM-D total followed by graphic presentation (Figures 1a-1e) of the results of the HAM-D total and the 4 secondary outcome variables. Statistical comparisons were not provided by the sponsor.

Treatment*	Endpoint 03 mean (se)	6 weeks mean (se)	3 months mean (se)	6 months mean (se)	9 months mean (se)	1 year mean (se)
Crossovers						
Parox (imi)	23.4 (0.6)	17.6 (0.9)	11.0 (1.0)	11.0 (1.6)	7.5 (1.6)	5.6 (1.0)
Imi (parox)	22.5 (0.6)	15.0 (1.0)	11.2 (1.2)	11.0 (1.9)	7.1 (1.3)	7.4 (1.4)
Parox (placebo)	25.0 (0.3)	15.2 (0.8)	9.0 (0.6)	9.6 (1.0)	7.7 (0.7)	8.6 (1.1)
Continuations						
Parox (Parox)	9.9 (0.5)	10.2 (0.7)	10.0 (0.8)	9.5 (0.9)	10.2 (1.3)	9.8 (1.3)
Imipramine (Imi)	8.7 (0.7)	8.4 (0.7)	8.3 (0.8)	8.6 (0.8)	8.1 (1.1)	6.8 (1.4)
Placebo (plac)	10.1 (0.7)	9.7 (0.9)	10.4 (1.1)	9.7 (1.5)	6.8 (1.7)	6.3 (1.8)

* PAR 03 treatment in parenthesis

The responses over time are consistent over all 5 variables. Non-responders who crossed over to paroxetine (imipramine and placebo non-responders) or imipramine (paroxetine non-responders) improved substantially over baseline. There is little difference between the three groups and the high proportion of dropouts taints statistical comparison.

The paroxetine, imipramine and placebo responders whose treatment was continued maintained their low depression ratings for one year. In these groups as with the crossovers, the high proportion of dropouts limits the interpretability of the results.

Comment

Although this study provides interesting data and is included by the sponsor among placebo controlled trials, it does not provide data addressing the advantage of paroxetine over placebo. The only comparison of paroxetine versus placebo follows a group of PAR 03 paroxetine, imipramine and placebo responders for a year and records similar relapse rates. This does not adequately demonstrate that paroxetine is effective in preventing relapse because the patients were not randomized at the beginning of the extension and because only 67% and 24% of the patients were still in the study at 3 months and 1 year.

Among the crossovers paroxetine and imipramine were equally efficacious in treating PAR 03 active drug non-responders. There is no control group for the placebo non-responders switched to paroxetine. High dropout rates and a possible confounding carryover effect proscribe inferences from the results in the crossover patients.

FIGURE V1.1

HAMD Total Means Across the Study by Treatment

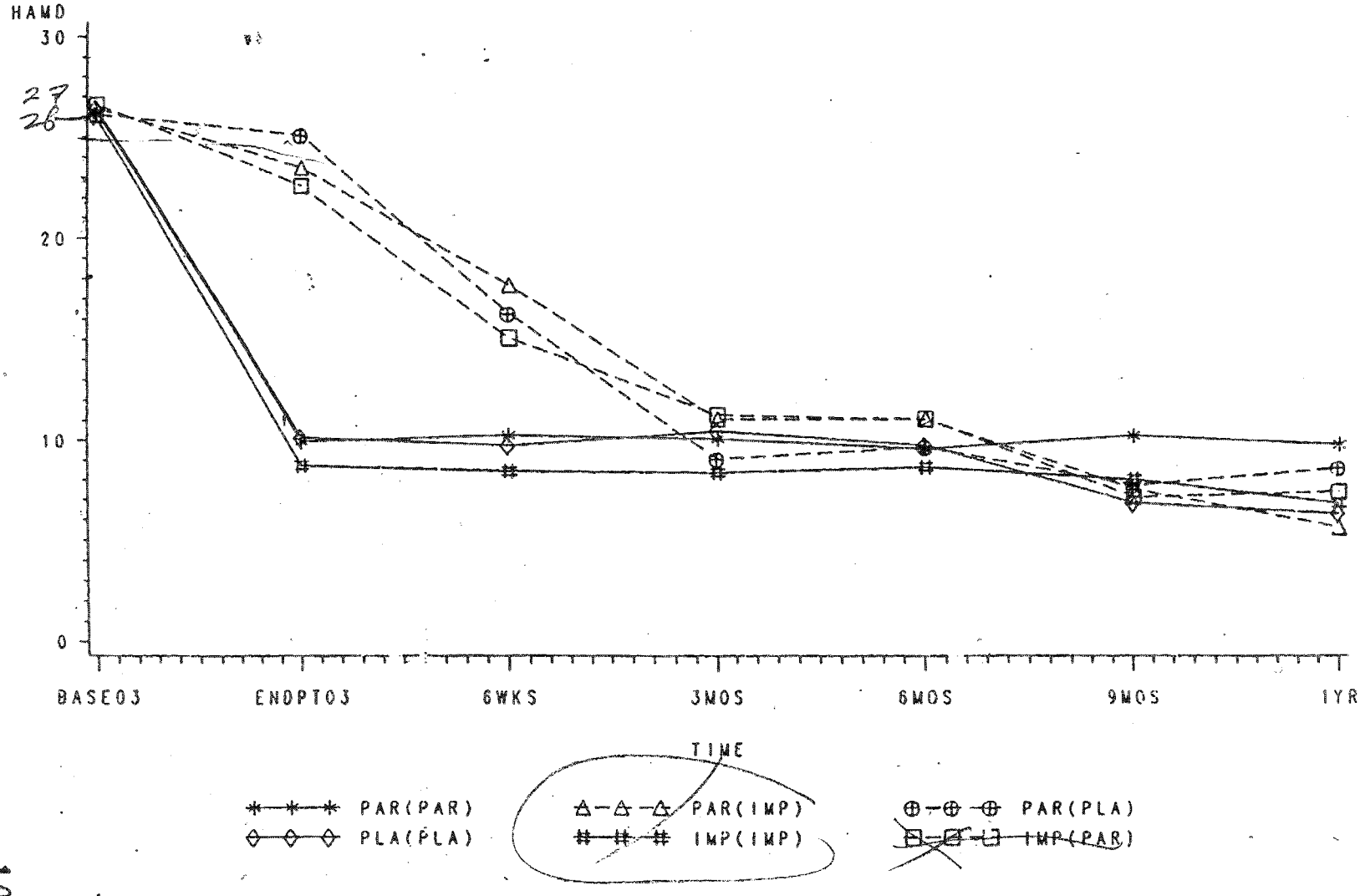

Figure 1A (Sponsor's figure)

FIGURE V1.3

HAMD Depressed Mood Item Means Across the Study by Treatment

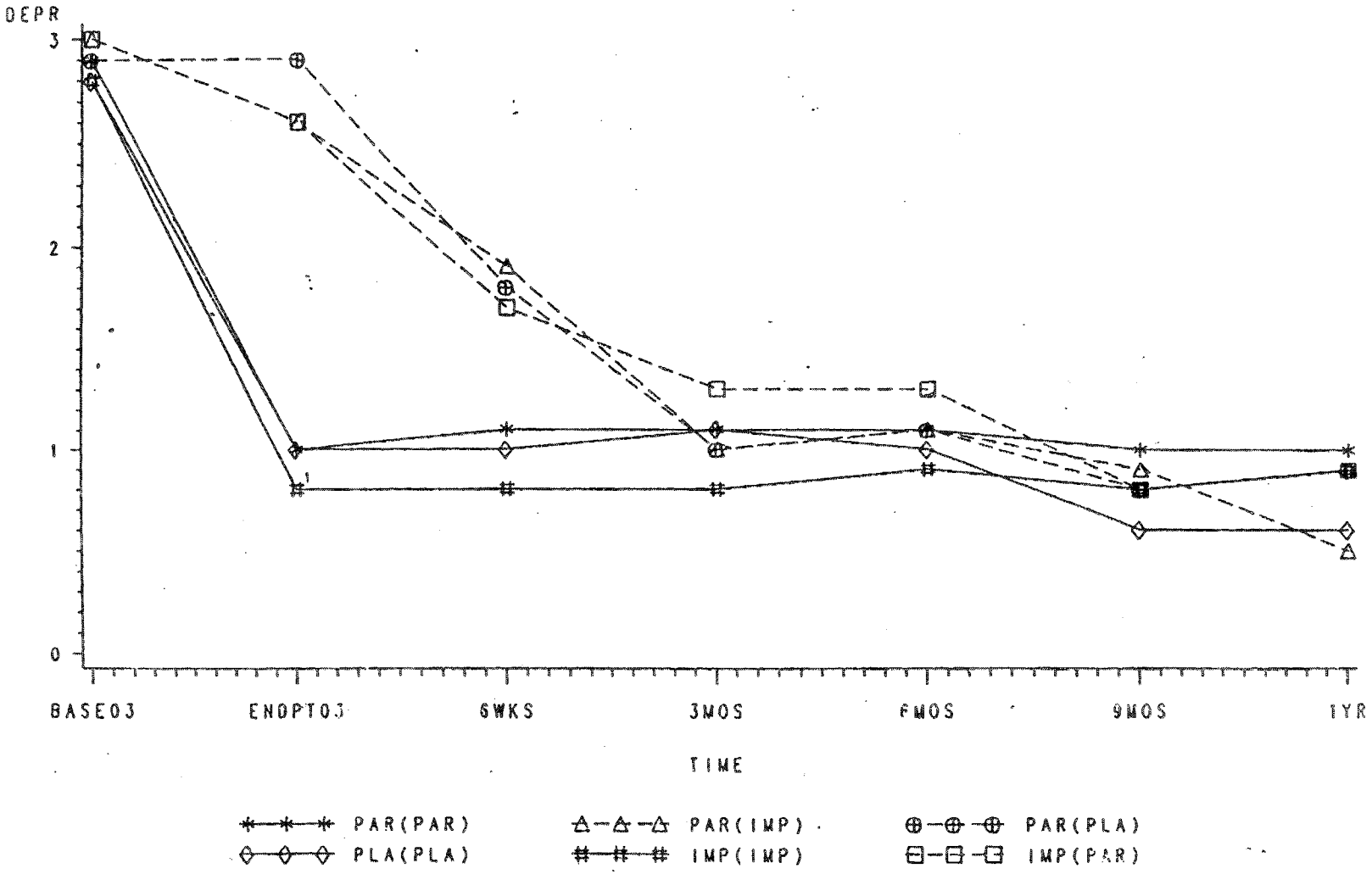

Figure 1c (Sponsor's figure)

FIGURE V1.4

SCL Factor IV Depression Means Across the Study by Treatment

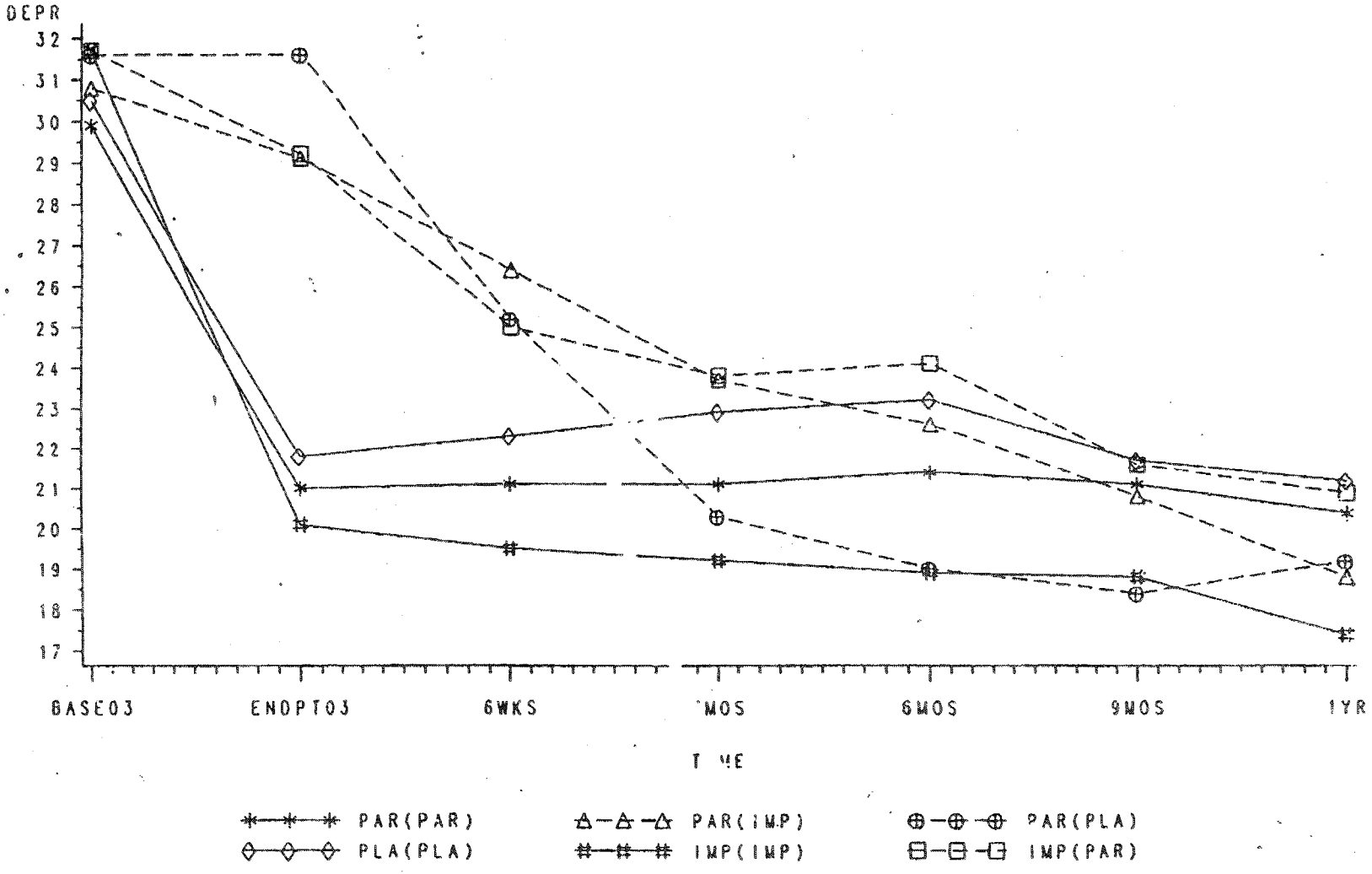

Figure 1d (Sponsor's figure)

FIGURE V1.5

CGI Severity of Illness Means Across the Study by Treatment

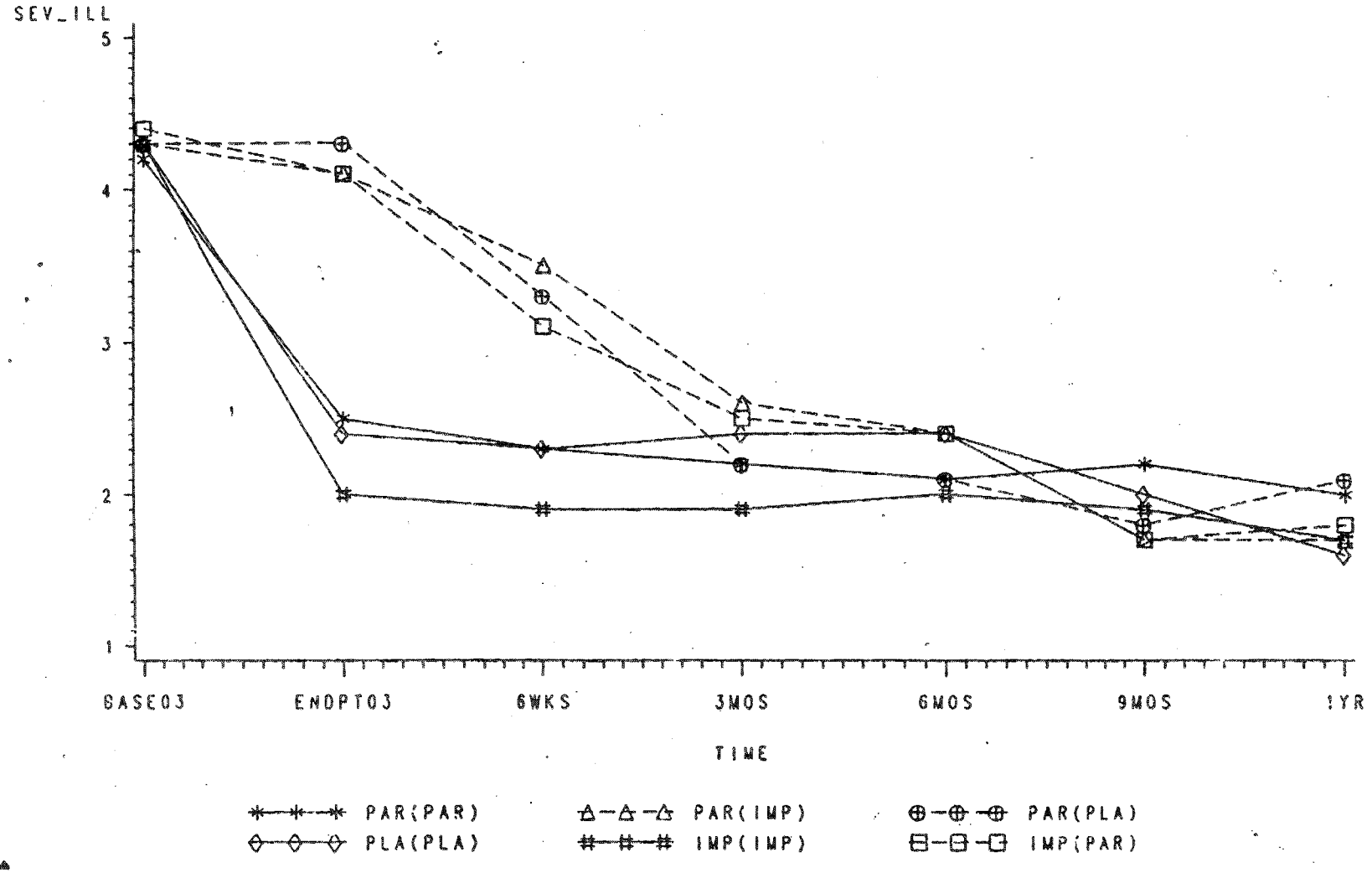

Figure 1e (Sponsor's figure)

Analysis of covariance with HAM-D total score as the dependent variable revealed only one treatment by covariate interaction. Patients experiencing their first episode of depression (as opposed to a recurrent episode) who received 10 mg of paroxetine improved less than other groups. This finding is difficult to interpret and probably represents random variation.

Treatment X Investigator interactions for all six variables in both the Intent to Treat and 1 week completer data sets were all greater than 0.1.

Comment
The most prominent finding in this trial was that 20mg was the most efficacious dose of paroxetine. The fixed dose protocol without titration to target dose prevented dose optimization and led to more early dropouts in the 30 and 40 mg groups compared to 20 mg. The disproportion in early discontinuations biased the results against the higher dose groups.

This study was not designed to provide pivotal evidence of paroxetine's superiority over placebo. The number of significant comparisons versus placebo, while not by themselves convincing, support data from other trials which demonstrated paroxetine's efficacy.

PLACEBO CONTROLLED TRIALS; FOREIGN STUDIES

06; G. J. Naylor, Principal Investigator

This was a 4 week, single center, double blind, placebo controlled trial of paroxetine 30 mg HS vs. placebo in patients with depression.

Subjects
Subjects were 18-65 years old with a diagnosis of depression diagnosed by Feighner's criteria and who had a score of at least 18 on the 21 item Hamilton scale for depression. After patient 20 was enrolled the Hamilton inclusion threshold was lowered to 17. Patients with severe co-existing disease, current or past evidence of organic brain syndrome, who had received ECT within the past month, who were considered at risk for suicidal acts or gestures or who were known abusers of drugs or alcohol were excluded. Pregnant and lactating women were also excluded.

Following a baseline evaluation and a 7 day washout patients were randomized to placebo or 30 mg paroxetine to be taken at HS. Day 1 of the study was defined as the first day patients received drug or placebo which occurred as much as two weeks after the baseline examination. Unlike the previously described U.S. studies a second assessment was not performed to exclude patients who spontaneously improved.

Flunitrazepam was prescribed for insomnia. Patients were assessed after 1, 2 and 4 weeks. The outcome variables were the 21 item Hamilton depression scale, an observer-completed 6 point global assessment scale, a patient completed Beck Depression Inventory and a patient completed self rating visual analog scale. (Visual analog data was not submitted).

The sponsor defined a standard Intent to Treat population and a smaller "Efficacy" group which differed from the Intent to Treat group insofar as they met

PAR 07; Ward Smith, David Dunner, Ferris Pitts, Principal Investigators

This was a multicenter, six week, double-blind, randomized, parallel placebo and amitriptyline controlled trial in inpatients with moderately to severe depression with melancholia. The study was initiated in Octob and terminated 10 months later because of low patient enrollment.

Subjects and Design

Patients were at least 18 years old, had to meet DSM-III criteria for melan have a score of at least 21 on the first 17 items of the Hamilton Sca Depression and have a Raskin Depression Scale score greater than their s the Covi Anxiety Scale. Exclusion criteria were similar to the pr protocols.

Prior to the start of active treatment there was a single blind screening/ period of at least 4 days. Patients could be discharged from the hospital a minimum of one week of active treatment. Outcome measures were the sam the previous studies.

The dose range was 1-6 capsules morning and evening with initial dosing be capsules at each time. Paroxetine capsules were 10 mg in the morning and in the evening while the amitriptyline capsules were 25 mg on both occ Medication was titrated by changing both the morning and evening dose capsule.

Results

Enrollment was limited to 24, 5 and 9 patients at each of the three site number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	13	13 (100%)	11 (85%)	11 (85%)	9 (69%)	8 (62%
Placebo	12	12 (100%)	9 (75%)	9 (75%)	9 (75%)	7 (58%
Amitriptyline	13	13 (100%)	13 (100%)	13 (100%)	12 (92%)	11 (85%

There were no significant between group differences on any efficacy mea 4 or 6 weeks by either the LOCF or visitwise analysis. On all the key va there was a trend favoring paroxetine over both amitriptyline and placeb study had a 10% chance of detecting a 20% difference at week 6.

Comment

This trial, included in the service of completeness, is too small t meaningful inference.

PAR 09

[redacted]

This was a multicenter, 12 week, double blind, placebo controlled study of [redacted] 10, 20, 30, 40mg) of paroxetine in adult outpatients with mode moderately [redacted] depression without mania.

Subjects and Design

The admission criteria were [redacted] same as in PAR 03 except for the hyper exclusion which was omitted. As in [redacted] ceding protocols there was a 7 day washout for patients on any psychotropic [redacted] ation and a 14 day placebo

PAR 07; Ward Smith, David Dunner, Ferris Pitts, Principal Investigators

This was a multicenter, six week, double-blind, randomized, parallel placebo and amitriptyline controlled trial in inpatients with moderately to severe depression with melancholia. The study was initiated in October and terminated 10 months later because of low patient enrollment.

Subjects and Design
Patients were at least 18 years old, had to meet DSM-III criteria for melancholia, have a score of at least 21 on the first 17 items of the Hamilton Scale for Depression and have a Raskin Depression Scale score greater than their score on the Covi Anxiety Scale. Exclusion criteria were similar to the previous protocols.

Prior to the start of active treatment there was a single blind screening/washout period of at least 4 days. Patients could be discharged from the hospital after a minimum of one week of active treatment. Outcome measures were the same as the previous studies.

The dose range was 1-6 capsules morning and evening with initial dosing being 2 capsules at each time. Paroxetine capsules were 10 mg in the morning and 20 mg in the evening while the amitriptyline capsules were 25 mg on both occasions. Medication was titrated by changing both the morning and evening dose by one capsule.

Results
Enrollment was limited to 4, 5 and 9 patients at each of the three sites. The number of patients remaining in the study at each assessment point were:

Treatment	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6
Paroxetine	13	13 (100%)	11 (85%)	11 (85%)	9 (69%)	8 (62%)
Placebo	12	12 (100%)	9 (75%)	9 (75%)	9 (75%)	7 (58%)
Amitriptyline	13	13 (100%)	13 (100%)	13 (100%)	12 (92%)	11 (85%

There were no significant between group differences on any efficacy measure at 4 or 6 weeks by either the LOCF or visitwise analysis. On all the key variables there was a trend favoring paroxetine over both amitriptyline and placebo. The study had a 10% chance of detecting a 20% difference at week 6.

Comment
This trial, included in the service of completeness, is too small to support meaningful inference.

PAR 09

This was a multicenter, 12 week, double blind, placebo controlled study of 3 doses (10, 20, 30, 40mg) of paroxetine in adult outpatients with moderate to moderately severe depression without mania.

Subjects and Design
The admission criteria were the same as in PAR 03 except for the hyperthyroid exclusion which was omitted. As in preceding protocols there was a 7 day placebo washout for patients on any psychotropic medication and a 14 day placebo

for patients on a MAOI. Previously unmedicated patients had a 4-10 day placebo washout.

Patients were randomized in blocks of nine consisting of one patient to receive placebo and two patients at each of the paroxetine doses. Patients took their medication in the morning and were assessed at days 7, 14, 21, 28, 42, 63 and 84. There was no titration to assigned dose. The protocol specified the primary endpoint at 42 days after which patients who felt they were responding could continue for another 6 weeks. The primary outcome variable was the HAM-D total. The secondary variables were the HAM-D retardation factor and depressed mood item, the SCL depression factor, the CGI severity of Illness and the MADRS. The Covi, Raskin and Patient Global Evaluation scales were also administered.

Results

474 patients entered the double blind phase of whom 454 had at least one efficacy evaluation which may have occurred after less than one week of treatment. The mean age was 41 years. The proportion of male patients in the five groups ranged from 44-53%. There were no significant ($p<.05$) between group differences on any of 44 demographic, historical or diagnostic variables or in the proportion of patients whose treatment was interrupted. The number of patients remaining at each timepoint were:

Treatment	Week 1	Week 2	Week 3	Week 4	Week 6	Week 9	Week 12
Placebo	51 (100%)	47 (92%)	43 (84%)	39 (76%)	34 (67%)	23 (45%)	21 (41%)
Parox 10mg	102 (100%)	91 (89%)	82 (80%)	77 (75%)	71 (70%)	53 (52%)	46 (45%)
Parox 20mg	104 (100%)	93 (89%)	92 (88%)	83 (80%)	68 (65%)	54 (52%)	44 (42%)
Parox 30mg	101 (100%)	83 (82%)	70 (69%)	66 (65%)	61 (60%)	44 (44%)	40 (40%)
Parox 40mg	102 (100%)	84 (82%)	78 (76%)	69 (68%)	65 (64%)	56 (55%)	48 (47%)

73% of the entire sample remained at week 4; 65% remained at week 6. Week 4, the last timepoint with 70% of subjects remaining will be highlighted as the primary endpoint. Data collected after week 6 is biased by non-randomization and a high dropout rate.

There were no significant between group differences at baseline for any efficacy variable. Change from baseline results from the week 4 Intent to Treat population Last Observation Carried Forward were:

Week 4, LOCF, Intent to Treat

Variable	Placebo N=51	10 mg N=100	20 mg N=104	30 mg N=99	40 mg N=100	p-value** Treatment	Invest.	Linear
HAM-D Total	-8.23	-7.58	-10.57+	-9.00	-9.39	0.048	<.001	.166
Retardation	-2.33	-2.38	-3.08+	-2.52	-2.91	0.154	<.001	.152
Depressed Mood	-0.93	-1.06	-1.27*	-1.18	-1.24	0.180	<.001	.037
CGI Severity	-1.00	-0.76	-1.24+	-1.01	-1.06+	0.039	<.001	.248
SCL Depression	-4.27	-4.42	-6.78*+	-5.59	-5.54	0.351	.166	.098
MADRS Score	-8.90	-8.26	-12.13*+	-10.19	-11.14+	0.017	.002	.050

*p<.05 vs. placebo; +p<.05 vs. 10mg;
**Treatment X Investigator interaction term deleted from the statistical model

$7.58 \times 100 = 758$
$10.57 \times 104 = 1099$
$9 \times 99 = 891$
$9.39 \times \frac{100}{403}$ $\quad 939$
$3687/403 = 9.14$

For all 6 variables the peak effect occurred at 20 mg and decreased at higher doses. A similar LOCF table was constructed for patients who completed one week of treatment. These data showed the same pattern as the Intent to Treat sample, but the p values were smaller. The Intent to Treat sample showed a slightly weaker paroxetine effect than the one week completers because it carried forward the scores of patients, predominantly paroxetine dropouts for adverse experiences, who dropped out in the first week. For all variables but the HAM-D total and the MADRS the week 6 results showed a stronger paroxetine effect than at week 4 for both the Intent to Treat group and the 1 week completers. The results tabulated above are therefore the least favorable to paroxetine. The week 6 results from the one week completers, the data most favorable to paroxetine, shows the 20, 30 and 40 mg doses all superior to 10 mg paroxetine on the HAM-D total, retardation factor, depressed mood item and CGI severity and the 40 mg dose also superior to placebo on the HAM-D retardation factor and depressed mood item.

Between group comparisons can arguably be made using any of these 4 data sets (week 4 or week 6, Intent to Treat or one week completer). 12 comparisons can therefore be made between the 20mg, 30mg and 40 mg groups and the placebo or the 10 mg group. The following table lists the number of significant comparisons between the "adequate" dose groups (20, 30 and 40mg) versus placebo and versus 10mg.

Number of Significant Comparisons 20, 30 and 40mg (Maximum 12)

Variable	vs. placebo	vs.10mg	Comment
HAM-D Total	1	7	Effect vs placebo in 20mg paroxetine group
Retardation Factor	2	5	Effect vs placebo in 20mg paroxetine group
Depressed Mood Item	9	5	
CGI Severity	0	11	
SCL Depression	4	4	All 8 significant comparisons in group who received 20 mg paroxetine
MADRS	2	10	Effect vs placebo in 20mg paroxetine group

There were no significant differences on any comparison between the 20mg and the 30mg or 40mg groups, between the 30mg and the 40mg groups or between the 10mg and placebo groups. The summary table, particularly the comparison against placebo, highlights the peak effect of 20 mg paroxetine in this trial. This conclusion is consistent with the mean improvement scores which were highest in the 20 mg paroxetine group.

Visitwise analyses at 4 and 6 weeks, submitted in response to FDA request, showed maximum efficacy for the 20 mg dose at 6 weeks with a less clear cut advantage at 4 weeks. Only 2 of 36 comparisons versus placebo (3 doses X 2 timepoints X 6 variables) showed a significant advantage versus placebo.

Among one week completers there was a significant treatment effect at 4 and 6 weeks on the proportion of patients who improved by at least 50%. This resulted from a significantly decreased proportion of 50% responders in the 10 mg group compared to the higher paroxetine dosages. There was no significant differences in the proportion of 50% responders between placebo and any of the paroxetine doses. There was no treatment effect on the proportion of 50% responders in the 4 and 6 week Intent to Treat data.

both studies patients had to have Raskin depression scores greater than Covi anxiety scores and could not have a decline in depression ratings of 20% or greater between screen and baseline visit. Exclusion criteria for medical illness and washout interval from other psychotropics were the same as in the placebo controlled trials.

Patients were titrated to doses of 10-40 mg/d of paroxetine and 50-200 mg/d of doxepin. The only psychotropic medication permitted was chloral hydrate for insomnia. Mean daily dose of paroxetine was 23.4 mg; mean endpoint paroxetine dose was 22.7 mg.

Results

Enrollment varied from 9 patients at the smallest site to 42 patients at the largest. The total Intent to Treat sample had 136 paroxetine and 135 doxepin patients balanced in their demographic, historical and diagnostic characteristics. 67% of the paroxetine and 71% of the doxepin patients completed the study with similar reasons for discontinuation in each group. The changes from baseline were similar to those observed in the controlled trials with younger patients.

Change From Baseline- Intent to Treat Sample- LOCF

Outcome Variable	Paroxetine		Doxepin		RMS Error	p-value
	N	Mean	N	Mean		
HAMD Total	132	-9.87	132	-9.78	7.55	0.92
HAMD Retardation Factor	132	-2.92	132	-2.63	2.61	0.36
HAMD Depressed Mood	132	-1.37	132	-1.05	---	0.01
SCL Depression	128	-4.84	125	-5.00	6.22	0.84
MADRS	131	-11.63	131	-11.12	8.97	0.65
CGI Severity of Illness	132	-1.36	131	-1.17	1.12	0.16

NO placebo

58 of 132 (44%) patients in each group showed an improvement of 50% or more in their HAMD total scores.

Comment

Although this trial did not contain a placebo group and did not provide an analysis of investigator by drug interactions, it provides a measure of assurance that the efficacy observed in placebo controlled trials also obtains in older patients.

Other Studies

The sponsor also presented data from 6 active controlled European trials in geriatric patients. 3 of these trials enrolled less than 10 patients in each cell. In the other 3 trials paroxetine 20 or 30 mg/d was compared to clomipramine 60-75 mg/d or mianserin 60 mg/d. There was no significant advantage for either compound in any of the three trials, but there was improvement over baseline for all 6 patient groups.

UNCONTROLLED TRIALS

The sponsor reported on 18 open trials of which only 8 had at least 10 completers. Efficacy data was available from 16 of these studies all showing improvement with paroxetine. Two trials included plasma sampling and correlation with efficacy.

Analysis of covariance with HAM-D total score as the dependent variable revealed only one treatment by covariate interaction. Patients experiencing their first episode of depression (as opposed to a recurrent episode) who received 10 mg of paroxetine improved less than other groups. This finding is difficult to interpret and probably represents random variation.

Treatment X Investigator interaction for all six variables in both the Intent to Treat and 1 week completer data sets were all greater than 0.1.

Comment

The most prominent finding in this trial was that 20mg was the most efficacious dose of paroxetine. The fixed dose protocol without titration to target dose prevented dose optimization and led to more early dropouts in the 30 and 40 mg groups compared to 20 mg. The disproportion in early discontinuations biased the results against the higher dose groups.

This study was not designed to provide pivotal evidence of paroxetine's superiority over placebo. The number of significant comparisons versus placebo, while not by themselves convincing, support data from other trials which demonstrated paroxetine's efficacy.

PLACEBO CONTROLLED TRIALS; FOREIGN STUDIES

UK 06; G. J. Naylor, Principal Investigator

This was a 4 week, single center, double blind, placebo controlled trial of paroxetine 30 mg HS vs. placebo in patients with depression.

Subjects

Subjects were 18-65 years old with a diagnosis of depression diagnosed by Feighner's criteria and who had a score of at least 18 on the 21 item Hamilton scale for depression. After patient 20 was enrolled the Hamilton inclusion threshold was lowered to 17. Patients with severe co-existing disease, current or past evidence of organic brain syndrome, who had received ECT within the past month, who were considered at risk for suicidal acts or gestures or who were known abusers of drugs or alcohol were excluded. Pregnant and lactating women were also excluded.

Following a baseline evaluation and a 7 day washout patients were randomized to placebo or 30 mg paroxetine to be taken at 10PM. Day 1 of the study was defined as the first day patients received drug or placebo which occurred as much as two weeks after the baseline examination. Unlike the previously described U.S. studies a second assessment was not performed to exclude patients who spontaneously improved.

Flunitrazepam was prescribed for insomnia. Patients were assessed after 1, 2 and 4 weeks. The outcome variables were the 21 item Hamilton depression scale, an observer-completed 6 point global assessment scale, a patient completed Beck Depression Inventory and a patient completed self rating visual analog scale. (Visual analog data was not submitted).

The sponsor defined a standard Intent to Treat population and a smaller "Efficacy" group which differed from the Intent to Treat group insofar as they met the

inclusion/exclusion criteria and did not receive psychotropic medication other than flunitrazepam.

Results

The Intent to Treat group consisted of 22 paroxetine patients and 23 placebo patients whose mean age was 41 of whom 29% were male. 61% of placebo patients and 33% of paroxetine patients had a previous depression (p=.068). The placebo patients also had higher (p=.007) anhedonia scores and melancholia factor scores (p=.024) at baseline than the paroxetine patients. Mean baseline HAM-D total score was 24. 10 paroxetine patients and 3 placebo patients discontinued.

With 3 minor exceptions there were no significant paroxetine-placebo differences on change from baseline for any variable at any timepoint in either the Intent to Treat or the Efficacy data sets analyzed by either LOCF or visit-wise methods. The exceptions were week 2 visitwise comparisons where paroxetine was superior on the global assessment in the efficacy data set and on the Beck Inventory in the efficacy and Intent to Treat data sets. Change in Ham-D total scores at week 4 were minimally higher in the paroxetine than in the placebo group in the visitwise data and minimally higher in the placebo patients in the LOCF data set.

Comment

This low power study did not show paroxetine to be an effective antidepressant. If the results had been significant, inference would be limited because of the failure to eliminate spontaneous improvers, the delay between baseline assessment and the initiation of treatment and the failure of randomization to produce fully matched groups.

UK 09; J. G. Edwards, Principal Investigator

[redacted] was a 6 week, randomized, double blind, parallel group study of paroxetine 30mg [redacted] night vs. placebo in outpatients with depression.

Subjects [redacted]nd Design

Patients [redacted]e 18-65 years of age who were suffering from unipolar or bipolar depressive i[redacted]ness, whose illness was characterized as "autonomous" insofar as it was largely i[redacted]pendent of environmental influences. The inclusion criteria specified a HAM-[redacted]otal score of at least 15 at enrollment and at least 12 at the start of blinded [redacted]atment. These criteria differ from previous studies in allowing bipolar pa[redacted]nts and having a lower threshold on the HAM-D total. Exclusion criteria were [redacted]imilar to previously described trials.

Patients received a 4-7 da[redacted] placebo washout before beginning on either 30 mg paroxetine or placebo to be ta[redacted]n at night. Concomitant psychoactive medication was proscribed except for a sho[redacted] acting benzodiazepine for insomnia. Patients were assessed at 1, 2, 4 and 6 w[redacted]s on the Hamilton Depression Scale, Global Assessment Scale, Leeds Self-assessm[redacted] Scale, a self rating visual analog scale and a clinician's overall efficacy sca[redacted]

Results

The Intent to Treat sample comprised 41 patie[redacted] (20 paroxetine), mean age 44 and 44% male who did not differ on demographic, h[redacted]orical or baseline variables. Despite the low threshold for inclusion, mean HAM-[redacted] total score was 26. Only 10 paroxetine and 7 placebo patients (41% of the Intent[redacted]o Treat sample) completed

inclusion/exclusion criteria and did not receive psychotropic medication other than flunitrazepam.

Results

The Intent to Treat group consisted of 22 paroxetine patients and 23 placebo patients whose mean age was 41 of whom 29% were male. 61% of placebo patients and 33% of paroxetine patients had a previous depression (p=.068). The placebo patients also had higher (p=.007) anhedonia scores and melancholia factor scores (p=.024) at baseline than the paroxetine patients. Mean baseline HAM-D total score was 24. 10 paroxetine patients and 3 placebo patients discontinued.

With 3 minor exceptions there were no significant paroxetine-placebo differences on change from baseline for any variable at any timepoint in either the Intent to Treat or the Efficacy data sets analyzed by either LOCF or visit-wise methods. The exceptions were weekly visitwise comparisons where paroxetine was superior on the global assessment in the efficacy data set and on the Beck Inventory in the efficacy and Intent to Treat data sets. Change in Ham-D total scores at week 4 were minimally higher in the paroxetine than in the placebo group in the visitwise data and minimally higher in the placebo patients in the LOCF data set.

Comment

This lower study did not show paroxetine to be an effective antidepressant. If the results had been significant, inference would be limited because of the failure to eliminate spontaneous improvers, the delay between baseline assessment and the initiation of treatment and the failure of randomization to produce fully matched groups.

UK 09; J. G. Edwards, Principal Investigator

This was a 6 week, randomized, double blind, parallel group study of paroxetine 30mg at night vs. placebo in outpatients with depression.

Subjects and Design

Patients were 18-65 years of age who were suffering from unipolar or bipolar depressive illness, whose illness was characterized as "autonomous" insofar as it was largely independent of environmental influences. The inclusion criteria specified a HAM-D total score of at least 15 at enrollment and at least 12 at the start of blinded treatment. These criteria differ from previous studies in allowing bipolar patients and having a lower threshold on the HAM-D total. Exclusion criteria were similar to previously described trials.

Patients received a 4-7 day placebo washout before beginning on either 30 mg paroxetine or placebo to be taken at night. Concomitant psychoactive medication was proscribed except for a short acting benzodiazepine for insomnia. Patients were assessed at 1, 2, 4 and 6 weeks on the Hamilton Depression Scale, Global Assessment Scale, Leeds Self-assessment Scale, a self rating visual analog scale and a clinician's overall efficacy scale.

Results

The Intent to Treat sample comprised 41 patients (20 paroxetine), mean age 44 and 44% male who did not differ on demographic, historical or baseline variables. Despite the low threshold for inclusion, mean HAM-D total score was 26. Only 10 paroxetine and 7 placebo patients (41% of the Intent to Treat sample) completed

6 weeks of treatment. There was no significant difference between paroxetine and placebo on the HAM-D total score or any factor score at any time point by either LOCF or visitwise analysis. Both the paroxetine and placebo groups showed progressive improvement over time with the paroxetine advantage approaching significance. There was a significant paroxetine advantage in the proportion of patients who improved by 50% in the LOCF analysis (p=.037), but not in the visit-wise comparison (p=.25). On the Global Assessment Scale paroxetine was superior to placebo on the visit-wise analysis, but not on the LOCF. Paroxetine was superior to placebo on the Leeds total score, specific depression and general depression scores. Paroxetine showed a significant effect on 2 of the 4 visual analog scales.

Comment

The small sample size, the high proportion of dropouts and the inconsistency of the findings between efficacy variables and between methods of analysis for the same efficacy variable render inference from this data hazardous. The data is supportive of other studies which showed paroxetine to be an effective antidepressant. The study is best classified as neither a "win" or a "loss", but rather as "equivocal".

UK 12; M. R. Trimble, Principal Investigator

This was a 6 week, two site, randomized, double blind, parallel group, pl[illegible]bo and mianserin controlled trial in depressed outpatients.

Subjects and Design

The submission did not include a protocol. Patients were 18[illegible] years of age with 17 item HAM-D scores of 15 or greater. They were diagn[illegible] as having unipolar depression, but diagnostic criteria were not specified. [illegible]e patients had been off other antidepressants for two weeks and were "consi[illegible]d suitable for tricyclic-like therapy". They received 30 mg of paroxetine [illegible] the morning or mianserin 30-90 mg in the evening or placebo. The protocol [illegible]scribed the use of psychoactive compounds other than oxazepam, a restriction [illegible]ich the investigator concedes was honored in the breach. Efficacy instr[illegible]nts were the HAMD and the Global Assessment.

Results

The number of subjects in the t[illegible] were:

	Entered			Completed		
	Paroxetine	Mi[illegible]erin	Placebo	Paroxetine	Mianserin	Placebo
N	19		10	12	11	6
Mean age	39.7	[illegible]2.7	51.6	39.6	41.9	55.1

The disparity i[illegible]roup sizes resulted from the refusal of the ethical committee at one site [illegible]llow the administration of placebo. The protocol was rewritten for that s[illegible], but the data was combined.

There [illegible]e no between group differences on the HAM-D total scores, any of the fact[illegible] scores or the Global Assessment at 4 and 6 weeks.

6 weeks of treatment. There was no significant difference between paroxetine and placebo on the HAM-D total score or any factor score at any time point by either LOCF or visitwise analysis. Both the paroxetine and placebo groups showed progressive improvement over time with a paroxetine advantage approaching significance. There was a significant paroxetine advantage in the proportion of patients who improved by 50% in the LOCF analysis (p=.037), but not in the visit-wise comparison (p=.25). On the Global Assessment Scale paroxetine was superior to placebo on the visit-wise analysis, but not on the LOCF. Paroxetine was superior to placebo on the Leeds total score, specific depression and general depression scores. Paroxetine showed a significant effect on 2 of the 4 visual analog scales.

Comment

The small sample size, the high proportion of dropouts and the inconsistency of the findings between efficacy variables and between methods of analysis for the same efficacy variable render inference from this data hazardous. The data is suggestive of other studies which showed paroxetine to be an effective antidepressant. The study is best classified as neither a "win" or a "loss", but rather as "equivocal".

UK 12; M. R. Trimble, Principal Investigator

This was a 6 week, two site, randomized, double blind, parallel group, placebo and mianserin controlled trial in depressed outpatients.

Subjects and Design

The submission did not include a protocol. Patients were 18-70 years of age with 17 item HAM-D scores of 15 or greater. They were diagnosed as having unipolar depression, but diagnostic criteria were not specified. The patients had been off other antidepressants for two weeks and were "considered suitable for tricyclic-like therapy". They received 30 mg of paroxetine in the morning or mianserin 30-90 mg in the evening or placebo. The protocol proscribed the use of psychoactive compounds other than oxazepam, a restriction which the investigator concedes was honored in the breach. Efficacy instruments were the HAMD and the Global Assessment.

Results

The number of subjects in the trial were:

	Entered			Completed		
	Paroxetine	Mianserin	Placebo	Paroxetine	Mianserin	Placebo
N	19	16	10	12	11	6
Mean age	39.7	42.7	51.6	39.6	41.9	55.1

The disparity in group sizes resulted from the refusal of the ethical committee at one site to allow the administration of placebo. The protocol was rewritten for that site, but the data was combined.

There were no between group differences on the HAM-D total scores, any of the factor scores or the Global Assessment at 4 and 6 weeks.

Comment
This study was seriously flawed by the refusal of the ethical committee at one of the sites to allow the administration of placebo and by the widespread use of psychoactive medication proscribed by the protocol. Given the small sample size it is hardly surprising that neither active treatment was superior to placebo.

MDUK 14; P. Tyrer, Principal Investigator

This study was included among the placebo controlled trials although the "placebo control" referred to a two or four week placebo phase either before or after 6 weeks of active treatment. There were only 30 patients in the Intent to Treat sample and statistical analysis was not performed. This data cannot address the question of efficacy.

ACTIVE CONTROLLED TRIALS

General Population

The sponsor presented data from 34 active controlled trials, mostly of six weeks duration, all of which were conducted abroad. Most of these trials had less than 10 subjects in each cell. In 11 of the studies there was no significant differences between amitriptyline 100-150 mg/d, mianserin 30-90 mg/d or imipramine 150 mg/d and paroxetine 30 mg/d. In two studies there was no significant difference in HAM-D total scores, but significant differences in retardation factor and melancholic factor scores which favored paroxetine over mianserin in one trial and amitriptyline over paroxetine in the other. In two trials comparing paroxetine 30 mg to an inadequate dose of amitriptyline (75 mg/d), paroxetine was superior in one case and no difference was observed in another. In two continuation trials with limited participation there was no difference in relapse rates. In one trial, DFG-119 DUAG, clomipramine was superior to paroxetine.

DFG-119 DUAG
This was a randomized, double blind, parallel group, 6 week trial of paroxetine 30mg/d versus clomipramine 150mg/d conducted by the Danish University Antidepressant Group.

Design
The subjects were depressed inpatients between 19 and 64 years of age with scores of 18 or more on the 21 item HAM-D or scores of 9 or more on a 6 item HAM-D subscale. Exact ICD diagnostic criteria were not provided. Exclusion criteria were similar to those employed in the placebo controlled trials including use of a MAOI within two weeks of active treatment and spontaneous improvement during the one week placebo washout.

Patients were titrated to 30 mg paroxetine or 150 mg clomipramine in three days. Lithium could be continued and oxazepam could be prescribed for sedation. Although exact characterization of concomitant medication was not provided some patients received ocher psychoactive medication during the study.

Results
The Intent to Treat sample included 60 patients randomized to paroxetine and 56 to clomipramine. 33 paroxetine and 30 clomipramine patients completed 6 weeks of treatment. 12% of the paroxetine and 18% of the clomipramine patients had

Comment
This study was seriously flawed by the refusal of the ethical committee at one of the sites to allow the administ[redacted] widespread use of psych[redacted] prescribed by the protocol. Given the small sample size [redacted] is hardly surprising that neither active treatment was superior to placebo.

MDUK 14; P. Tyrer, Principal Investigator

This study was included among the placebo controlled trials although the "placebo control" referred to a two or four week placebo phase either before or after 6 weeks of active treatment. There were only 30 patients in the Intent to Treat sample and statistical analysis was not performed. This data cannot address the question of efficacy.

ACTIVE CONTROLLED TRIALS

General Population

The sponsor presented data from 34 active controlled trials, mostly of six weeks duration, all of which were conducted abroad. 16 of these trials had less than 10 subjects in each cell. In 11 of the studies there was no significant differences between amitriptyline 100-150 mg/d, mianserin 30-90 mg/d or imipramine 150 mg/d and paroxetine 30 mg/d. In two studies there was no significant difference in HAM-D total scores, but significant differences in retardation factor and melancholic factor scores which favored paroxetine over mianserin in one trial and amitriptyline over paroxetine in the other. In two trials comparing paroxetine 30 mg to an inadequate dose of amitriptyline (75 mg/d), paroxetine was superior in one case and no difference was observed in another. In two continuation trials with limited participation there was no difference in relapse rates. In one trial, DFG-119 DUAG, clomipramine was superior to paroxetine.

DFG-119 DUAG
This was a randomized, double blind, parallel group, 6 week trial of paroxetine 30mg/d versus clomipramine 150mg/d conducted by the Danish University Antidepressant Group.

Design
The subjects were depressed inpatients between 19 and 64 years of age with scores of 18 or more on the 17 item HAM-D or scores of 9 or more on a 6 item HAM-D subscale. Exact ICD-9 diagnostic criteria were not provided. Exclusion criteria were similar to those employed in the placebo controlled trials including use of a MAOI within two weeks of active treatment and spontaneous improvement during the one week placebo washout.

Patients were titrated to 30 mg paroxetine or 150 mg clomipramine in three days. Lithium could be continued and oxazepam could be prescribed for sedation. Although exact characterization of concomitant medication was not provided some patients received ocher psychoactive medication during the study.

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The Intent to Treat sample included 60 patients randomized to paroxetine and 56 to clomipramine. 33 paroxetine and 30 clomipramine patients completed 6 weeks of treatment. 12% of the paroxetine and 18% of the clomipramine patients had

(8)

Statistical Review and Evaluation

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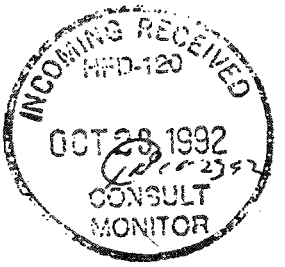

NDA #: 20-031 / Drug Class 1S

Applicant: SmithKline Beecham Pharmaceuticals

Name of Drug: PAXIL[1] (paroxetine hydrochloride)

Indication: Treatment of depression.

Documents Reviewed: Volumes 1.450, 1.661.1 and 1.477 to 1.543. Amendments dated 2/19/91, 6/27/91 and 3/9/92. Medical review of Dr. Martin Brecher (HFD-120) dated June 3, 1991 and statistical review of Kenneth Petronis (HFD-713), issued simultaneously with this review.

Medical Input: Thomas Laughren, M.D. (HFD-120) has been consulted during the process of this review.

Background

The sponsor has presented in this submission the results of both placebo-controlled and active-controlled studies conducted in the USA and in foreign countries to show the efficacy and safety of paroxetine in the treatment of depression. The focus of this review will be 6 studies conducted under Protocol PAR 03. These 6 studies, all conducted in the USA, consisted of three treatment arms: paroxetine, placebo and imipramine. Other characteristics of these studies are discussed in the next section of this review entitled "General Comments on the PAR 03 Studies". Five additional USA studies were conducted under Protocols PAR 01 and PAR 02. The design of these five studies was similar to the design of the PAR 03 studies except these studies had no active control arm. A statistical review of these studies was completed by Mr. Ken Petronis (HFD-713).

In addition to the USA studies, the sponsor has submitted the results of over 40 foreign studies. Approximately 30 of these studies were active-controlled studies with generally less than 40 patients enrolled in each study. The active controls used in these studies were clomipramine, amitriptyline, mianserin, maprotiline and imipramine. Four foreign studies were placebo-controlled studies. Like the active-controlled studies, these studies were small studies with usually less than 20 patients in each arm. Three of the placebo-controlled trials were reviewed by Dr. Martin Brecher (HFD-120) and found to provide inconclusive evidence of efficacy due to the small sample sizes and design flaws. None of these foreign studies will be discussed in this review.

The sponsor conducted one trial (PAR 09) to establish the minimum effective dose of paroxetine. This trial is discussed in the section of this review titled "Dosing". Dr. Brecher also reviewed this study.

In addition to the efficacy studies, the sponsor conducted several studies designed to address specific issues related to the use of paroxetine, such as, in-patient use (PAR 07), morning versus evening dosing (UK study by Wade), long-term use (PAR 04), correlation between plasma concentration and effect (foreign study conducted by Vangtorp and Meidahl) and relapse (Study 29060/III/083/MC). These studies will be discussed by this reviewer in an addendum to this review.

Keywords: benefit-risk relationship, depression, dropouts, minimum effective dose, active control.

[1] The trade name was originally Aropax.

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TABLE 1
PLACEBO CONTROLLED DOUBLE BLIND RANDOMIZED TRIALS

Protocol # Investigator	Win/Lose Duration	N° Baseline HAM-D	M.E.D.@ IP/OP+	Site	Outcome at Endpoint
U.S.					
PAR 01-001	L	48	35mg/d	Single	No effect on HAMD or HAMD
Cohn;	6 weeks	28	OP		factors, CGI, Zung, or MADRS.
PAR 02-001	W	104	35mg/d	Single	Effective on HAM-D total, HAMD
Rickels;	6 weeks	26	OP		depression item, CGI.
PAR 02-002	W	71	35mg/d	Single	Effective on HAM-D total, HAMD
Claghorn;	6 weeks	25	OP		Retardation Factor, CGI.
PAR 02-003	L	66	43mg/d	Single	No significant effect on any
Smith;	6 weeks	29	OP		outcome variable.
PAR 02-004	W	78	37mg/d	Single	Paroxetine superior to placebo
Dilev;	6 weeks	28	OP		on most measures weeks 4 and 6.
PAR 03-001	W	118	30mg/d	Single	Not effective in ITT sample;
Feighner;	6 weeks	25	OP		effective All Efficacy group.
PAR 03-002	L	120	37mg/d	Single	Significant efficacy on most
Cohn;	6 weeks	25	OP		measures in all analyses.
PAR 03-003	L	124	34mg/d	Single	No demonstrable advantage for
Mendels;	6 weeks	26	OP		paroxetine over placebo.
PAR 03-004	?	120	40mg/d	Single	Results equivocal; trend — obscure, uncertain, misleading
Shrivastava;	6 weeks	27	OP		favors paroxetine.
PAR 03-005	W	119	38mg/d	Single	Paroxetine superior to placebo.
Fieve;	6 weeks	27	OP		Imipramine beats paroxetine.
PAR 03-006	W	116	35mg/d	Single	High dropout rate; paroxetine
Fabre;	6 weeks	29	OP		effective vs. placebo.
PAR 04	NA	503	35mg/d	6 sites	Study design does not allow - extension of Par 03
Feighner	1 year	23	OP		inference regarding efficacy.
PAR 07	L	38	20mg/d	6 sites	Study had insufficient power;
Smith	6 weeks	30	IP/OP		trend favored paroxetine.
PAR 09	?	454	NA	10 sites	Fixed dose study. 20 mg most
Feighner	6weeks	25	OP		efficacious dose.
Foreign					
UK006	L	45	30mg/d	Single	Low power flawed study.
Naylor	4 weeks	24	OP		
UK009	?	41	30mg/d	Single	Low power study, high dropout
Edwards	6 weeks	26	OP		rate, equivocal results.
UK012	W	45	30mg/d	2 sites	Low power, methodologically
Trimble	6 weeks	22	OP		flawed study.

* Total all cells; @ Mean Endpoint Dose; + Inpatient or Outpatient

PAR 05 was a long term, open U.S. trial in which patients showed substantial improvements from baseline in all outcome variables. 353 patients were enrolled of whom 130 completed 1 year of treatment. This study provided paroxetine plasma levels in patients in different outcome categories. Median plasma levels were:

6 week responders 58.7 ng/ml; 6 week non-responders 54.0 ng/ml;
all responders 50.75 ng/ml; relapsers 49.95 ng/ml.

The lack of separation in the plasma levels of responders and non-responders is reflected in the non-significant correlation coefficient of -.07 for the plasma level-HAMD Total score relationship.

RAD/PAR/C3 was an open Danish study in which 18 subjects received 40-80 mg/d for 4 weeks. Mean steady state plasma concentrations (SD) were:

40 mg/d - 65 (34) ng/ml; 60 mg/d - 124 (65) ng/ml; 80 mg/d - 157 (78) ng/ml.
No relationships were observed between steady state paroxetine concentration and final HAMD total score.

Studies MDUK 41 and 42 compared morning and evening doses of 30 mg of paroxetine. There was no difference in outcome assessed by the HAMD and CGI Severity, but more insomnia was observed with the evening dose.

INTEGRATED EFFICACY SUMMARY

The 14 U.S. and 3 U.K. placebo controlled trials provide convincing evidence for the short term efficacy of paroxetine in treating depression. Of these studies the 11 trials conducted under protocols 01, 02 and 03 provide the pivotal demonstration of efficacy. The protocol for these trials specified outpatients meeting DSM-III criteria for depression and having HAMD total scores of at least 18. These patients had mean baseline HAMD total scores in the 25-29 range justifying their characterization as being moderately severe to severely depressed. 4 of the 6 other placebo controlled trials (PAR 07 and the 3 U.K. trials) were insufficiently powered and the remaining 2 (PAR 04 and PAR 09) were not designed to address the issue of short term efficacy. Table 1 includes summary results of these trials.

except

In 6 trials (02-001, 02-002, 02-004, 03-001, 03-005 and 03-006) paroxetine was clearly superior to placebo. In 03-004 the paroxetine group improved more than the placebo patients, but the statistical results were equivocal. In 3 other trials (01-001, 02-003 and 03-002) the paroxetine patients showed non-significant greater improvement than their cohorts on placebo. In one trial (03-003) the improvement in the paroxetine and placebo groups were almost equal. The chance probability of 6 of 10 trials being significant at the .05 level is 2.7×10^{-6}.

The clear demonstration of efficacy in the 6 "win" trials is buttressed by the results in Par 09, the fixed dose trial, which showed trends favoring paroxetine at doses of 20 mg and higher.

Figures 2A and 2B summarize the differences between paroxetine and placebo at 4 and 6 weeks on the HAMD total in the Intent to Treat patients assessed by LOCF. In all but one of the pivotal trials (Mendels, PAR 03-03) the paroxetine patients improved more than the placebo patients. In the small UK study conducted by

Naylor the placebo patients improved more than the paroxetine group on the LOCF but not the visitwise analysis.

The sponsor classified the 11 trials conducted under protocols 01, 02 and 03 as providing pivotal evidence of efficacy if there was a significant difference between paroxetine and placebo on the HAMD total and the CGI severity at 4 weeks by LOCF analysis in the Intent to Treat population. The data from 5 trials (02-01, 02-04, 03-01, 03-05 and 03-06) met this standard. Par 02-02, which was counted as a "win" did not qualify as a pivotal trial under the sponsor's categorization rule because the paroxetine advantage was not significant at week 4. Trials were considered supportive if any two of the primary efficacy variables (HAMD total, HAMD retardation factor, HAMD depressed mood, CGI severity, SCL depression factor and MADRS) showed a significant paroxetine advantage (Intent to Treat, LOCF) at either 4 or 6 weeks. 3 studies (2-02, 03-02 and 03-04) met this criterion. Studies which did not meet either of the above criteria were classified as equivocal. 5 trials (01-01, 02-03, 03-03, UK06 and UK09) fell into this category.

The 6 head to head comparisons of imipramine and paroxetine in the PAR 03 series show paroxetine to be at least as efficacious as imipramine. Mean week 4 improvement in HAMD total scores (LOCF) was greater in the paroxetine group in 5 of the 6 trials. Paroxetine and imipramine each showed a significant advantage in one trial. Mean week 6 improvement in HAMD totals (LOCF) showed paroxetine superior to imipramine in 4 of 6 trials with each compound having a significant advantage in one study. The mean changes from baseline in HAMD total scores were:

	Week 4 (Intent to Treat, LOCF)					Week 6 (Intent to Treat, LOCF)				
Study	Paroxetine		Imipramine		p	Paroxetine		Imipramine		p
	Mean	N	Mean	N		Mean	N	Mean	N	
Shrivastava	-10.4	37	-5.8	40	.01*	-11.49	37	-6.38	40	.01*
Fieve	-9.6	40	-14.6	36	.01**	-10.02	40	-15.56	36	.02**
Feighner	-9.8	39	-7.2	40	.08	-10.77	39	-7.72	40	.06
Cohn	-8.0	40	-7.8	37	.90	-8.60	40	-9.59	37	.56
Mendels	-9.3	39	-7.8	41	.43	-9.90	39	-9.02	41	.68
Fabre	-7.8	39	-7.3	39	.72	-9.08	39	-7.62	39	.43

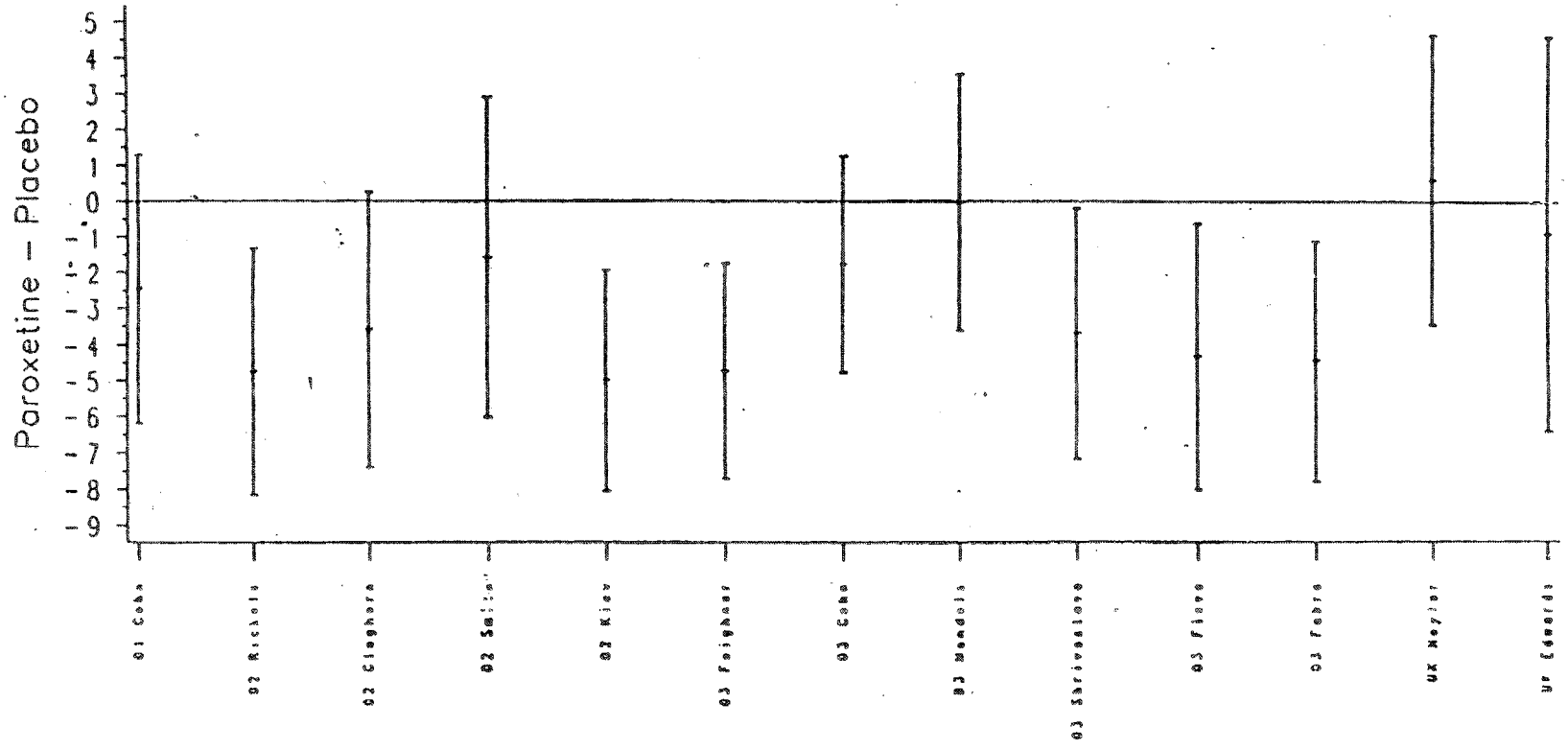
* paroxetine superior; ** imipramine superior

In these 6 studies the pooled proportion of paroxetine patients who improved by at least 50% on their HAMD total scores was 29.4% with 70% of subjects remaining (week 3 or 4) and 38.5% at week 6. The proportions for the imipramine patients was 21.2% and 35.3%. The difference approached significance at week 3-4.

The active control trials are supportive of paroxetine's efficacy insofar as patients on paroxetine and comparator were not statistically different and both groups improved. The open trials showing improvement provide additional, albeit weak, support of paroxetine's efficacy.

In each of the pivotal trials multiple comparisons were performed to detect baseline imbalances between treatment groups and treatment X covariate interactions. As expected from the number of statistical comparisons an occasional relationship was observed in a single study. However, no pattern of imbalance was detected nor did any pattern of covariation emerge. The incidental

Figure V.1
Difference Between Paroxetine and Placebo Means
Using HAMD Total −Baseline HAMD Total
Week 4, Extender Data Set
Intent−to−Treat Population



Vertical Lines Indicate 95% Confidence Limits Around the Mean

FIGURE 2A (Sponsor's figure)

Figure V.4
Difference Between Paroxetine and Placebo Means
Using HAMD Total −Baseline HAMD Total
Week 6, Extender Data Set
Intent−to−Treat Population

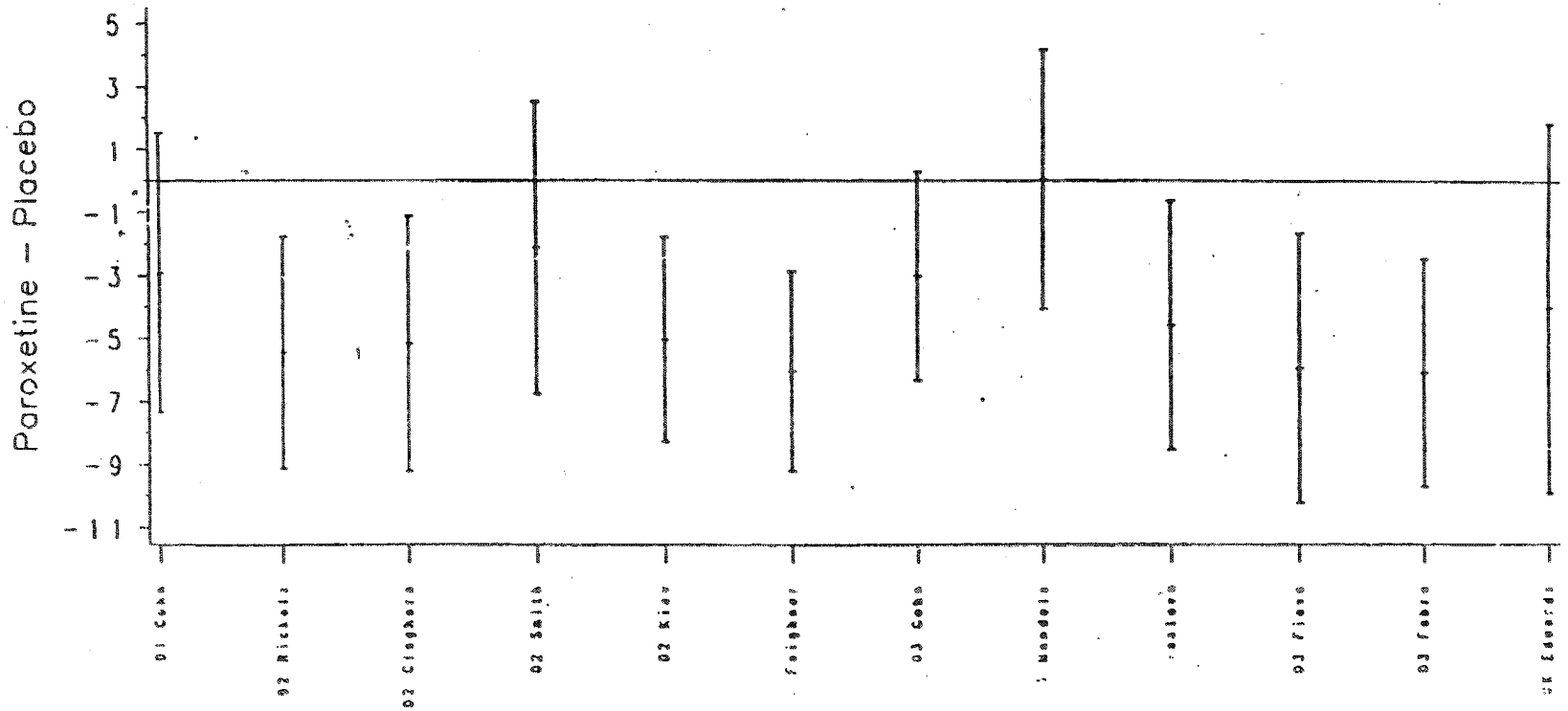


FIGURE 2B (Sponsor's figure)

significant result can be safely attributed to a chance result in a sea of observation.

Dosing and Efficacy

The protocols of the pivotal trials called for doses of 10-50 mg. The mean endpoint dose in these trials was generally in the 35-40 mg/d range. Mean changes from baseline in HAMD total scores (visitwise data set) from all patients in protocols 01, 02 and 03 were:

Dose	Week 4		Week 6	
	N	Change	N	Change
Placebo	296	-8.80	226	-10.10
10mg	7	-13.43	6	-12.33
20mg	42	-14.31	32	-15.81
30mg	57	-14.56	48	-16.02
40mg	64	-12.50	54	-14.65
50mg	142	-10.27	126	-13.13

This data shows a peak response at 30 mg which is not inconsistent with the peak response of 20 mg observed in fixed dose PAR 09. The somewhat smaller response at higher doses in variable dose trials represents upward dosing of slower or nonresponders. The difference in improvement in the 50mg/d group compared to placebo, 3 units on the HAMD total scale at week 6, is of the same magnitude as the paroxetine-placebo difference in these trials. The demonstration of efficacy in trials using a 10-50 mg dose range and the persistence of a therapeutic effect at 50mg/d allow the recommended dose range to extend to 50mg/d despite a higher incidence of adverse events at this dose.

Efficacy in Severe Depression

The sponsor pooled the paroxetine and placebo patients from PAR 01, 02 and 03 and divided them into those with baseline HAMD total scores of 27 or less designated as the moderately depressed group and those with HAMD total scores of 28 or greater designated as the severely depressed group. P-values for the Treatment X Severity interaction was .21 for the HAMD total and .18 for the CGI Severity scale. Means and paroxetine-placebo differences (LOCF) in the change at week 6 from baseline for the two variables were:

	HAMD Total				CGI Severity			
	Moderate	N	Severe	N	Moderate	N	Severe	N
Paroxetine	-9.90	256	-13.26	165	-1.19	256	-1.18	165
Placebo	-5.21	255	-8.77	166	-0.59	255	-0.84	166
Difference	3.79		4.49		0.60		0.34	
p-value	<.001		<.001		<.001		0.024	

Efficacy in Patients Older Than 65

A similar analyses of pooled data from all double blind trials conducted in the U.S. or Europe was done with age above and below 65 years as the categorical variable. Means and paroxetine-placebo differences (LOCF) in the change at week 6 from baseline were:

	HAMD Total				CGI Severity			
	≤65	N	≥65	N	≤65	N	≥65	N
Paroxetine	-11.32	1395	-10.69	248	-1.27	1245	-1.52	221
Placebo	-6.69	518	-8.90	21	-0.71	518	-0.86	21
Difference	4.63		1.79		.56		.66	
p-value	<.001		0.38		<.001		0.02	

The age X treatment interaction had a p-value of .18 for the HAMD total and .71 for the CGI Severity. The older group showed less improvement than the younger patients on the HAMD, but the opposite pattern was observed on the CGI. All of these comparisons are limited by the small number of patients older than 65 who received placebo.

Changes from baseline in pooled active control patients versus pooled paroxetine patients were:

	HAMD Total				CGI Severity			
	≤65	N	≥65	N	≤65	N	≥65	N
Paroxetine	-11.32	1395	-10.69	248	-1.27	1245	-1.52	221
Active Control	-12.38	810	-12.22	190	-1.30	653	-1.56	172
Difference	1.06		1.53		.03		.04	
p-value	.009		.08		.58		.80	

The treatment X age interaction had a p value .63 for the HAMD total and .99 for the CGI Severity.

An analysis of patients enrolled in geriatric studies in which the active control agent was doxepin showed no age X treatment effect and no significant differences between paroxetine and doxepin on the HAMD total or CGI in patients on either side of the 65 year cutoff.

Effect of Baseline Anxiety

The sponsor pooled all the Intent to Treat subjects in trials 01, 02 and 03 and dichotomized them into anxiety and no-anxiety groups on the basis of a baseline Covi Anxiety Score greater than 6. P-values for the Treatment X Anxiety interaction were .74 for the HAMD total and .55 for the CGI. Paroxetine was significantly superior to placebo as measured by change in HAMD total score (LOCF) and change in CGI score (LOCF) in both the anxiety and no-anxiety groups. The paroxetine advantage obtained with and without the inclusion of one center (Fieve) which was responsible for a significant Treatment X Anxiety X Investigator interaction.

Long Term Treatment

Long term data was obtained in U.S. trials PAR 04 (and extension) and 05 and in trials MDUK13, DFG119 Duag and HQMD II conducted overseas. The PAR 04 extension and the PAR 05 study were open trials and are therefore mute regarding paroxetine's long term efficacy. Only 17 of 41 patients who entered the PAR 04 extension remained after one year. The foreign trials were designed small and included only 13 paroxetine and 14 amitriptyline patients in MDUK13, 9 paroxetine and 4 clomipramine patients in DFG119 Duag and 75 paroxetine and 1 mianserin patient in HQMD II who were studied for one year.

In PAR 04 (reviewed above) there were very few differences in HAMD or CGI scores between the paroxetine, imipramine and placebo groups assessed 3, 6, 9 and 12 months after the conclusion of a 6 week short term trial. Only 105 of 503 (21%) patients who entered the long term phase remained in the trial for one year. The crude relapse rate was 12% for imipramine, 14% for paroxetine and 23% for placebo, but statistical analysis of Kaplan-Meier survival rates was not performed. Duration of response computed by the(Kaplan-Meier)method was 342.9 days for paroxetine, 156.7 days for imipramine and 121.5 days for placebo.

However, by failing to randomize patients at the beginning of the trial, PAR 04 is incapable by design of providing pivotal demonstration of long term efficacy. The placebo group consisted of the placebo responders from PAR 03 while both the paroxetine and imipramine groups included patients who continued to receive the same treatment as in PAR 03 and crossovers from the other active treatment. The paroxetine group also included crossovers from placebo. The data provide reassurance that the efficacy of paroxetine is not fleeting, but does not allow a claim regarding long term treatment. The efficacy of long term paroxetine treatment remains an open issue.

RECOMMENDATIONS FOR LABELING

Indications and Usage

The first sentence specifying an indication for severe depression and depression accompanied by anxiety should be replaced with "Paroxetine is indicated for the treatment of depression." This is the identical labeling for fluoxetine, the most recently approved antidepressant. The sponsor's conclusions regarding severity of depression and concomitant anxiety were derived from post-hoc analyses rather than clinical trials designed to address these issues. These retrospective analyses do not provide sufficient evidence for an indication.

The paragraph stating that efficacy is maintained for a year should be deleted. The long term studies described above were incapable by design of demonstrating long term efficacy.

Dosage and Administration

The statement "Tolerance to adverse experiences is rapid" should be deleted. This assertion is undefined, unsubstantiated by data and at variance with the summary statement in Volume 1.408 p. 43 which states that "Tolerance to most adverse experiences developed within one to three weeks of dosing for most patients."

The sponsor's recommendation that dosing in the elderly should begin at 20 mg should be revised downward to 10 mg. Elderly patients have twofold higher blood concentrations and greater interindividual variability than younger patients given the same dose. In trials PAR06 and PAR11 in which elderly patients were titrated to a clinically optimal dose, the mean endpoint dose was 23 mg/day which is substantially below the 30-43 mg/d range observed in the pivotal trials which excluded elderly patients.

The two paragraphs under the heading "Maintenance/Continuation/Extended Treatment should be deleted for lack of data from an adequate and well controlled trial.

BENEFIT-RISK ASSESSMENT

The benefits anticipated from the well documented efficacy of paroxetine unambiguously outweigh this drug's relatively benign side effect profile. Paroxetine was statistically superior to placebo in 5 or 6 well designed trials and trended in that direction in all but one of the remainder of the placebo controlled trials. No serious toxicities emerged in the course of an extensive clinical development program. The adverse experience profile, typical of the serotonin specific reuptake inhibitor class of antidepressants, provides an alternative to already marketed antidepressants and a therapeutic advantage for patients with abnormalities in cardiac conduction. If approved, paroxetine would be the third antidepressant of this class on the market. The large well organized data base in this application persuasively demonstrates that paroxetine is safe and effective.

Martin Brecher

Martin Brecher, M.D., D.M.Sc.
June 3, 1991

cc:
Original NDA 20-031
HFD-120
HFD-120/P Leber, T Laughren, M Brecher, P David

10-5-92

I have reviewed Dr. Brecher's findings and, in addition, I have reviewed the results of PAR 083, a relapse prevention trial. The safety and efficacy findings for paroxetine were presented to the PDAC on this date (10-5-92), and they unanimously agreed that paroxetine has been demonstrated to be safe and effective. I agree that, in the aggregrate, these data provide sufficient evidence of paroxetine's antidepressant efficacy to support its approvability. I will provide more detailed comments on efficacy issues in my supervisory memo, to follow. I have prepared the clinical sections of the draft SBA and the draft labeling that will accompany the approvable package.

Thomas P. Laughren, MD
Group Leader, PDP

the only one with results that consistently demonstrated paroxetine's superiority to placebo. Although its week 6 OC results were statistically insignificant (probably because less than 70 percent of placebo patients remained at week 6) its week 4 results were consistent across analyses. These findings indicated that the sponsor may have underanticipated the dropout rate for the 6 week period.

At week 4 there were 33 paroxetine and 27 placebo patients remaining in the trial. There was a considerable drop at week 6. Nine of the 33 paroxetine patients (27 percent) remaining at week 4 dropped out; 7 of the 27 (26 percent) placebo patients remaining at week 4 dropped out. Up until week 6 the dropout rate for each treatment group was not unusual. The sponsor offered no explanation for the sudden drastic dropoff at week 6. Demographic and clinical characteristics for the patients that left the trial between week 4 and week 6 should be provided by the sponsor in an attempt to explain why the dropout rate suddenly increased.

Reviewer's Conclusions (Which May Be Conveyed To The Sponsor)

Trial PAR 01-001 and the four trials in series PAR 02 were very similar in their design and in the measurements they employed but not in their results. Trials PAR 01-001 and PAR 02-003 failed to demonstrate that paroxetine was superior to placebo. Trial PAR 02-001 provided strong evidence of paroxetine's efficacy when analyzed as a single center trial; that strength was lost in the multicenter analysis. The sponsor provided no explanation for why the subcenter effects were so strong. The results of trial PAR 02-002 were generally favorable to paroxetine but were inconclusive; a statistically significant treatment difference for Ham-D Total was not found in every analysis. Only PAR 02-004 clearly demonstrated paroxetine's superiority to placebo on Ham-D Total, Ham-D Depressed Mood Item, and CGI Severity at week 4. At week 6, PAR 02-004 lost its power due to a sudden increase in the dropout rate.

All five trials used a target sample size of 72 patients for a single center and most enrolled a few less than 72. Only trial PAR 02-004 enrolled more than 72 patients in a single center; it was the only one with results that consistently demonstrated paroxetine's superiority to placebo. Although its week 6 OC results were statistically insignificant (probably because less than 70 percent of placebo patients remained at week), its week 4 results were consistent across analyses. These findings indicated that the sponsor may have underanticipated the dropout rate for the 6 week period.

S. Edward Nevius

for Kenneth R. Petronis, M.S., M.P.H.
Mathematical Statistician

Concur: Dr. Nevius [See Group Leader's Comments on following page.]

Dr. Dubey 9-11-92

cc:
Orig. NDA 20-031
HFD-120
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Mr. David
HFD-713/Dr. Dubey [File DRU 1.3.2]
HFD-713/Dr. Nevius
HFD-713/Ms.Mele
HFD-713/Dr. Takeuchi
HFD-713/Group 2 file
HFD-344/Dr. Lisook
Chron.

KRPetronis/SERB:krp:11/22/91; revised/sen:9/5/92

This review contains 14 pages plus 3 appended figures.

GROUP LEADER'S COMMENTS:

PAR 02-001 (Rickels): While the multicenter LOCF analyses of the HAM-D Total and Depressed Mood items were not as significant as the "single-center" analyses, they were still significant at the 5% level. Treatment reversals occurred only for the "combined" center (3 placebo patients, 6 paroxetine patients) and the Schweizer center (7 placebo, 4 paroxetine patients). I would consider the results of this study as supportive evidence of efficacy.

PAR 02-002 (Claghorn): Lack of significance for the OC analyses at week 6 may partly be attributed to power considerations; the HAM-D Total difference between paroxetine and placebo was approximately 5 units for both LOCF and OC analyses at week 6 but the power for detecting a five-unit difference from the OC analyses was only approximately .5. The dropout rates in both treatment groups was similar. I would consider the results of this study as supportive evidence of efficacy.

PAR 02-003 (Smith): The OC analyses which show paroxetine numerically worse than placebo are based on only 67% of the paroxetine patients and 43% of the placebo patients; only 16 placebo patients were observed at week 6. Therefore this treatment reversal in the OC analyses at week 6 should not be given undue emphasis; p-values from both LOCF and OC analyses at week 6 suggest that this study simply failed to distinguish paroxetine from placebo ($P \geq .35$ for both analyses). This study must, however, in the absence of an active control group to judge the adequacy of the test situation, be considered a negative study.

PAR 02-004 (Kiev): It might be noted that less than 55% of the placebo patients were observed at week 6; the power to detect a difference of the magnitude seen in the LOCF analyses (5 units) is less than .6. Thus the Week 6 results may be considered at least supportive of efficacy for paroxetine while the Week 4 results are strongly positive. I consider this study a positive study for the efficacy of paroxetine.

COMMENTS: The lack of inclusion of an active control in addition to the paroxetine and placebo groups makes interpretation of the PAR 02 studies difficult in cases where a clear superiority of paroxetine over placebo is not shown. The PAR 03 studies, reviewed by Joy Mele in a separate document, all have a three-way design with imipramine as an active control and are thus able to distinguish between a negative study (which fails to show a difference between test drug and placebo in a situation known to be capable of detecting a difference) and a failed study (which is incapable of detecting a difference between an known effective treatment and placebo). See Ms. Mele's conclusions for the PAR 03 studies; Table 28 of her review also presents an overview of results from both the PAR 02 and PAR 03 studies.

CONCLUSION: The results of the [redacted] document taken together with the [redacted] Mele in a separate review provide sufficient statistical evid[redacted]effectiveness of paroxetine for the treatment of derpession.

S. Edward Nevius

S. Edward Nevius, Ph.D.
Group 2 Leader

Table 28. HAM-D Total Mean Change from Baseline Week 4 LOCF Results
PAR 01, PAR 02 and PAR 03 Studies

STUDY	PAROXETINE			PLACEBO			p-value[1]	Stat. Evidence[2]
	N[3]	(%)[4]	HAM-D	N	(%)[4]	HAM-D		
01-001	24	(79%)	-12.9	24	(75%)	-10.4	.20	Negative
02-001[5]	43	(77%)	-11.6	44	(77%)	-7.4	.02	Supportive
02-002	36	(78%)	-10.2	34	(74%)	-6.6	.07	Supportive
02-003	39	(82%)	-8.9	37	(68%)	-7.4	.49	Negative
02-004	36	(92%)	-12.2	38	(71%)	-7.2	.002	Positive
03-001	39	(75%)	-9.8	37	(71%)	-5.1	.002	Positive
03-002	40	(68%)	-8.0	40	(55%)	-6.2	.25	Failed
03-003	39	(73%)	-9.3	42	(79%)	-9.2	.98	Failed
03-004	37	(73%)	-10.4	37	(63%)	-6.7	.04	Supportive
03-005	40	(78%)	-9.6	42	(79%)	-5.2	.02	Positive
03-006	39	(56%)	-7.9	37	(34%)	-3.4	.01	Positive

4 of 11 Significant

PAR 02 trials which did not show a difference between placebo and paroxetine are considered negative trials due to the lack of an active control group from which to assess the validity of the test situation.

The two PAR 03 trials which did not show a difference between placebo and paroxetine also did not distinguish imipramine from placebo suggesting a lack of sensitivity of the test situation. That is, since the trials themselves failed, the evidence against paroxetine could not be considered negative.

[1] Results of sponsor's ANOVA.

[2] The statistical evidence of efficacy showing paroxetine superior to placebo according to the statistical reviewer (Mr. Petronis for PAR 01 and 02 and Ms. Mele for PAR 03).

[3] N is the number of patients available for the Week 4 LOCF analysis.

[4] % is the percentage of patients still on study at Week 4.

[5] Excluding Dr. Clary's site results.

FIGURE 1. Percentage Of Patients On Study
All PAR 03 Studies Combined

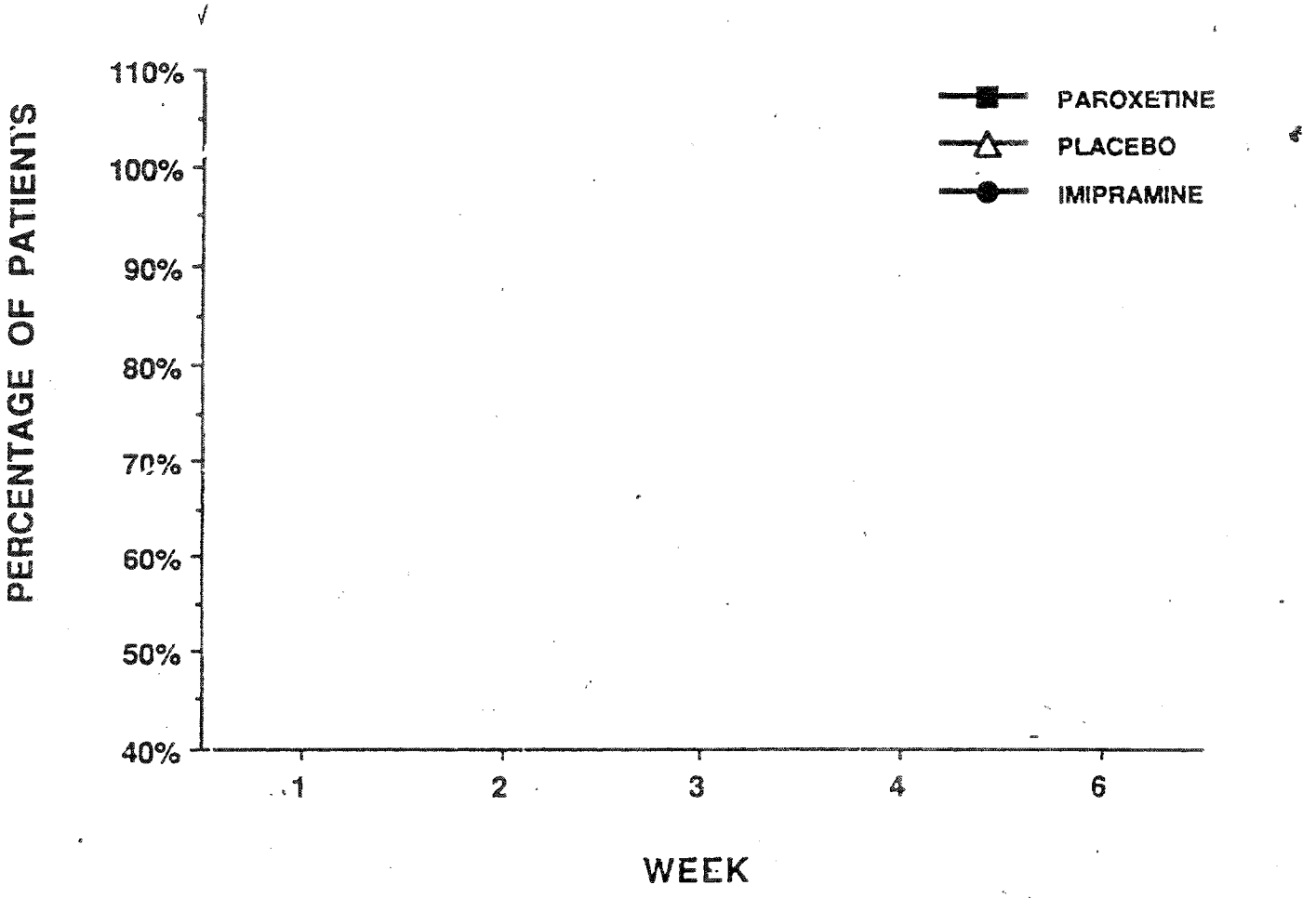
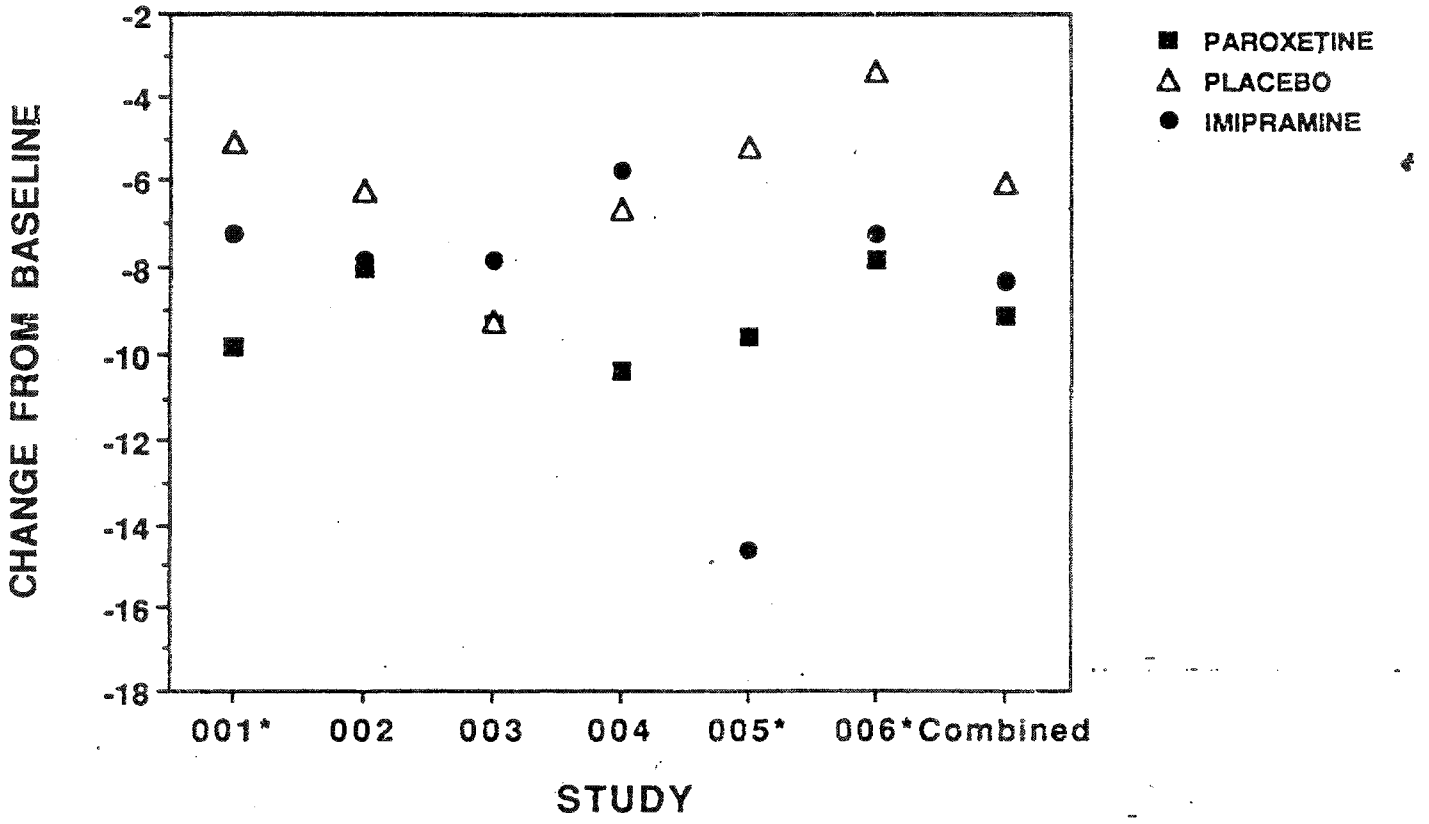


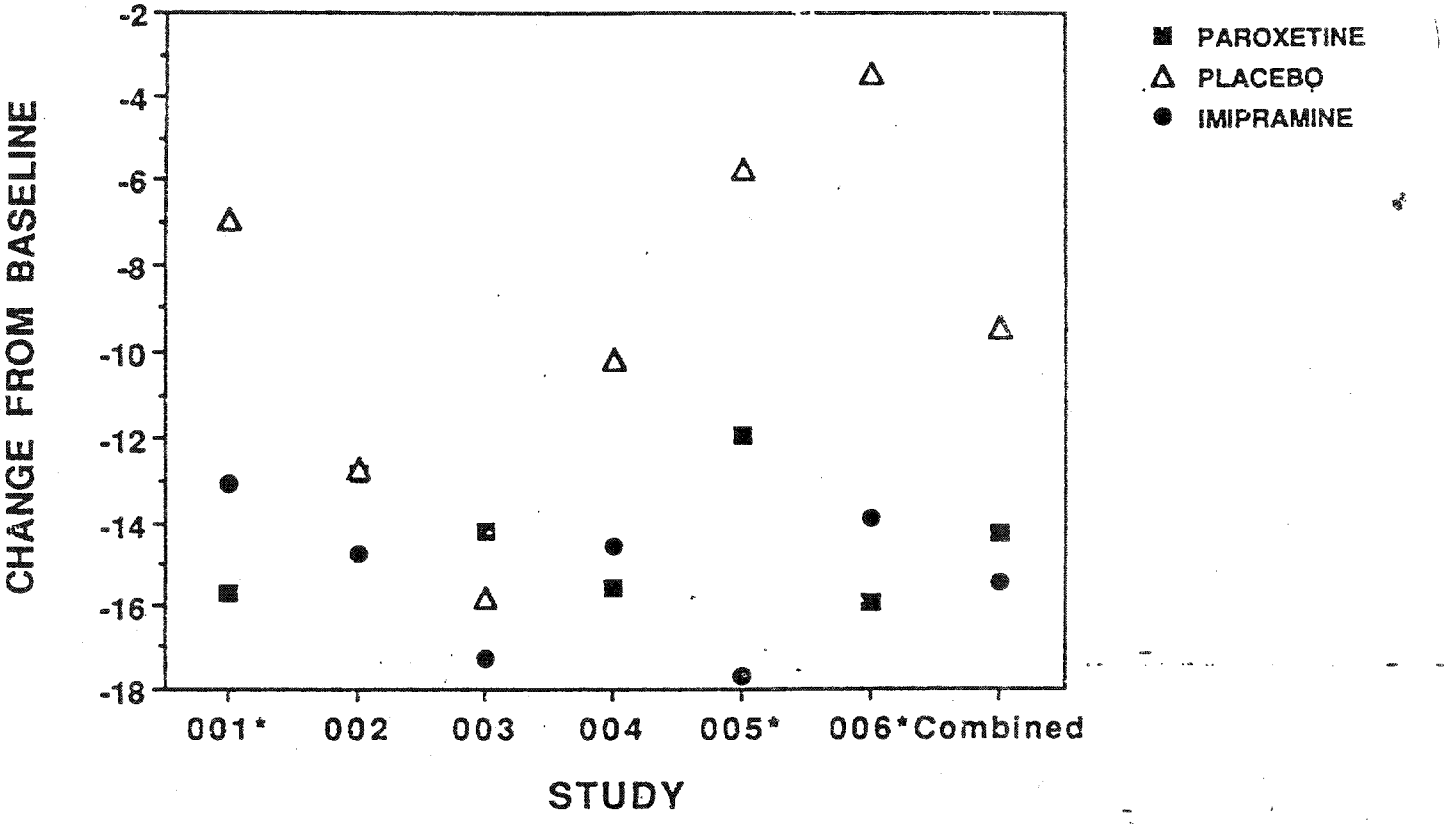
FIGURE 2. Sponsor's HAM-D Total Results
PAR 03 Studies
ITT Sample - Week 4 LOCF



Standard deviations for the means ranged from 6.1 to 8.9.

* Indicates positive trials

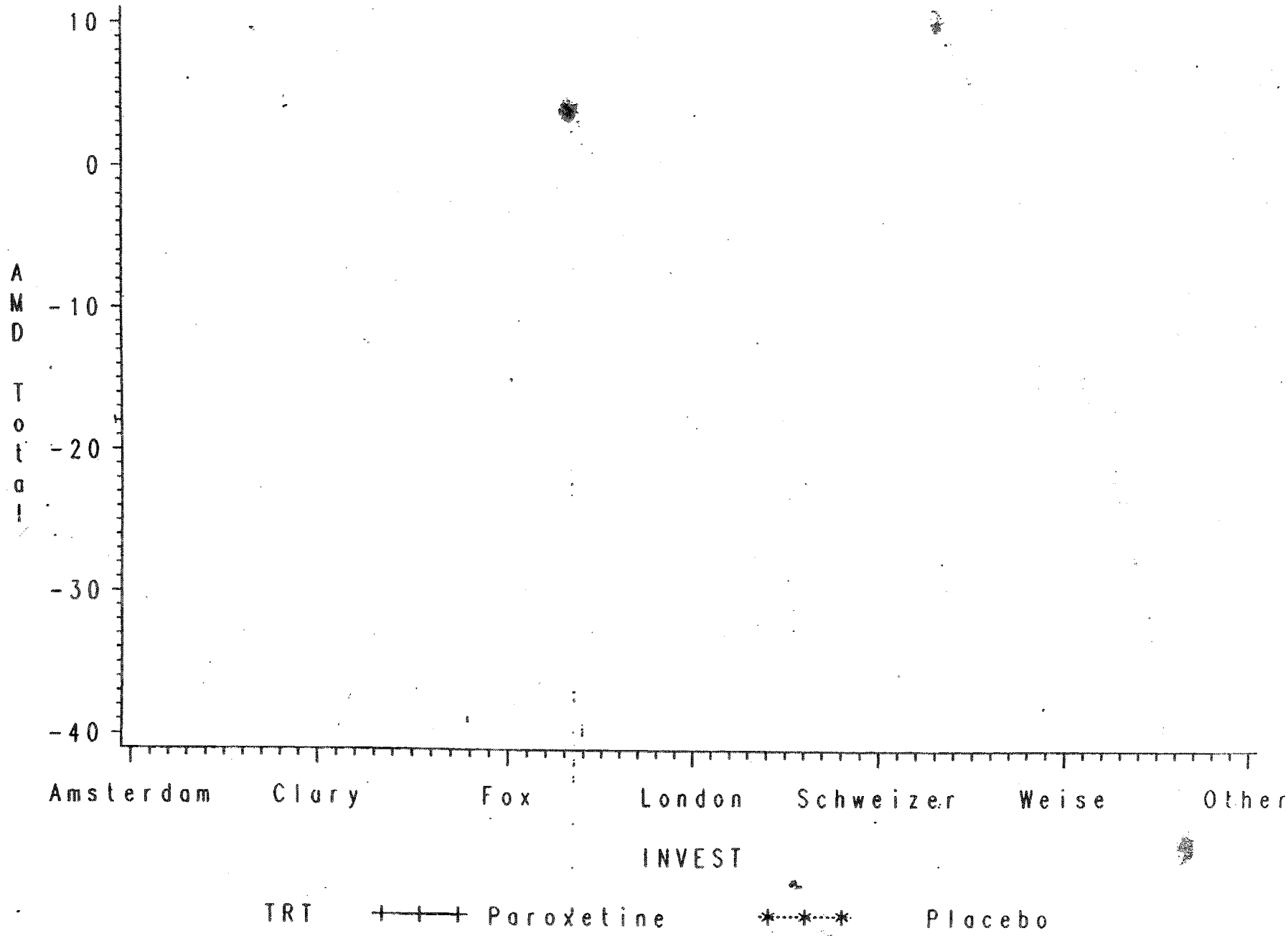
FIGURE 3. Sponsor's HAM-D Total Results
PAR 03 Studies
ITT Sample - Week 6 Completers



Standard deviations for the means ranged from 4.3 to 11.6.

* Indicates positive trials

Figure 1
Improvement from Baseline Extender Data Set, by Sub-investigator



Dosing

Dosing in PAR 03 Studies

For all studies conducted under the PAR 03 protocol, the starting dose for paroxetine was 20 mg/day and the starting dose for imipramine was 80 mg. Dosing could range from mg/day for paroxetine and from 65 to 275 mg/day for imipramine. Dosing was titrated to the optimum dose by increasing or decreasing the dose by 10 mg in the paroxetine group or 65 mg in the imipramine group.

The mean daily doses used in the PAR 03 studies and the mean doses recommended by the investigators for the two drug treatment groups are shown in the following table. For the 6 studies combined, approximately 30 mg/day of paroxetine was used while investigators recommended a higher dose of about 38 mg/day (which is approximately equal to the mean maximum dose used in these studies). From this data, there appears to be no clear relationship between the magnitude of the paroxetine dose administered and response, that is, the doses used in the positive trials are not distinguishable from the doses used in the other trials.

Table 26. Mean Daily Doses and Investigator Recommended Doses for PAR 03 Studies

	PAROXETINE		IMIPRAMINE	
STUDY	MEAN DAILY DOSE	RECOMMENDED DOSE	MEAN DAILY DOSE	RECOMMENDED DOSE
03-001*	26.1	30.5	110.4	156.8
03-002	30.9	39.5	140.9	193.8
03-003	27.8	36.9	133.5	197.8
03-004	32.1	45.5	138.5	188.3
03-005*	31.6	40.5	161.6	171.0
03-006*	28.5	37.1	134.5	187.3

* Positive trials which clearly show paroxetine to be superior to placebo.

It is interesting to note that the largest dose for imipramine was used in the study where the largest response to imipramine was observed, Study 03-005. This reviewer, however, did notice that this study had the highest percentage of males so that the dosing may have been related to weight. Therefore, this reviewer requested from the sponsor dosing information in mg/kg which was readily provided by the sponsor. The relative magnitude of the dosing was not altered by expressing the dose in terms of mg/kg. That is, Study 03-001 was still seen to have used the smallest dose, on average, Study 03-004, the largest paroxetine dose and Study 03-005, the largest imipramine dose. It may be, then, that the large imipramine response observed in Study 03-005 was due to the dose used.

Results of PAR 09

The sponsor has presented the results of a fixed dose, multicenter study, PAR 09. The objective of this study was to identify the lowest effective dose of paroxetine. Patients were randomized to one of 6 treatment groups; placebo or paroxetine at fixed doses of 10 mg, 20 mg, 30 mg or 40 mg at 10 centers. Twice as many patients were randomized to each paroxetine group compared to the placebo group (about 100 patients in each dose group and 50 patients in the placebo group). The ITT sample consisted of 454 patients with about 40 patients at each site. The study was conducted in two phases; Period I was a 6-week randomized double-blind phase followed by Period II which was another 6-week phase patients entered if they chose. So Period II data was from patients who were considered responders during Period I. (For more details regarding this trial see page 27 of Dr. Brecher's review.)

The efficacy results of patients completing Period I and those completing Period II are shown in the table below. (For the Week 4 LOCF results, see page 28 of Dr. Brecher's review). It is interesting to note that the percentage of patients still on study at 6 weeks and at 12 weeks is about the same for all groups. The reasons for discontinuing, however, did vary; the placebo patients dropped primarily due to lack of efficacy (16%) while the paroxetine groups dropped primarily due to adverse events (about 15% in the 10 and 20 mg group and about 25% in the 30 and 40 mg groups). The efficacy results for HAM-D total showed that the 20 mg, 30 mg and 40 mg groups were not different from placebo but were different from the 10 mg group. The largest significant response was seen in the 20 mg dose group; this was true across centers. These results were seen at 4 weeks as well as 6 weeks during Period I and for both the LOCF and OC analyses. Early dropouts in the 30 mg and 40 mg groups may have contributed to the lower LOCF response seen in these groups compared to the 20 mg group, however, it should be noted that the magnitude of the OC responses were larger in the 20 mg group than the higher doses as well. Clearly, these results show no trends in response related to dose.

Table 27. Completer Results for PAR-09

	Paroxetine Dose mg/day				
	0	10	20	30	40
Period I 6 Weeks					
N	33	70	68	61	65
(% of Enrolled)	(65%)	(69%)	(65%)	(60%)	(64%)
HAM-D Total Mean Change	-13.5	-10.8	-14.6	-13.4	-13.9
Period II 12 Weeks					
N	21	47	45	40	49
(% of Enrolled)	(41%)	(46%)	(43%)	(40%)	(48%)
HAM-D Total Mean Change	-15.7	-13.8	-17.2	-18.3	-15.6

Reviewer's Comments

The results from PAR 03 and PAR 09 suggest the following to this reviewer.

1. Doses of paroxetine less than 20 mg/day are not effective and may be detrimental.

2. The optimum dose of paroxetine is not known. Doses ranging from ng/day appear equally effective for the treatment of depression.

Summary and Conclusions

The sponsor has submitted the results of 11 USA efficacy trials conducted under the PAR 01, PAR 02 and PAR 03 protocols. The PAR 01 and PAR 02 studies had 2 treatment arms, paroxetine and placebo while the PAR 03 studies had 3 arms, paroxetine, placebo and imipramine. The designs for these 6-week trials were essentially the same. The PAR 01 and PAR 02 studies (a total of 5 studies) were reviewed by Mr. Ken Petronis (HFD-713) and will not be discussed in detail here. These trials are included in summary Table 28 for comparison. The focus of this section will be the results of the 6 PAR 03 studies reviewed by this statistician.

The results of the PAR 03 studies are summarized below.

1. The dropout patterns for the PAR 03 studies were similar. Placebo patients generally dropped due to lack of efficacy while drug-treated groups dropped primarily due to treatment-related adverse events. Figure 1 depicts the dropout rates for all the studies combined by treatment group. The drop seen in the drug groups, particularly imipramine, following one week of treatment, was due predominately to adverse events. The placebo patients usually discontinued after 3 weeks of therapy due to lack of efficacy. By Week 6, a higher percentage of patients in the paroxetine group compared to either the placebo or imipramine group remained on study attesting to a more favorable risk-benefit ratio for paroxetine compared to imipramine.

2. The small number of patients completing the studies (less than 60%) dictated basing conclusions primarily on LOCF analyses at Week 4. These results for the HAM-D total are summarized in Table 28 and depicted in Figure 2. Three of the PAR 03 studies (03-001, 03-005 and 03-006) were clearly positive. From Figure 2 it is readily apparent that the placebo response in the 3 positive trials is smaller than what was observed in the other 3 trials. The results for HAM-D depressed mood item and both CGI scales were consistent with the HAM-D total results in that paroxetine consistently beat placebo with p-values less than or equal to .04. The results from Study 03-004 were considered supportive because the HAM-D total results clearly favored paroxetine over placebo but the results from the other primary efficacy variables did not.

It is interesting to note that the imipramine response was more variable than the paroxetine response; this may be related to variability in the dropout patterns for imipramine.

3. The two trials (Studies 03-002 and 03-003) which failed to show paroxetine superior to placebo also failed to show imipramine superior to placebo. The latter suggests that the trials as designed or conducted were incapable of detecting important treatment differences. It is difficult to identify any unique characteristics about these trials which would yield negative results since some of the positive trials in this series have the same characteristics. For example, the large number of dropouts in each failed trial may have compromised the power of these trials, however, the trial (03-006) with the most dropouts yielded very positive results in favor of both drugs over placebo.

It is comforting to see that the magnitude of the HAM-D results for paroxetine (Table 28) are consistent with the results from the positive trials. Also, it should be noted that the PAR-01 and PAR-02 results are consistent with the PAR 03 results (Table 28).

4. Since all 6 PAR 03 studies were single center studies conducted under the same protocol, this reviewer combined their data to perform an overall analysis. An ANOVA model including an interaction term for treatment by center showed paroxetine to be statistically significantly better than placebo ($p < .001$) on all 5 primary efficacy variables. The interaction term was significant for the HAM-D depressed mood item, CGI severity illness and global improvement due to reversals of the treatment response in Study 03-003. When Study 03-003 data was excluded from the analysis, the interaction was no longer significant. (The means for HAM-D total for the combined data are shown in Figures 2 and 3.)

5. Since LOCF analyses may underestimate treatment effects, according to the dropout patterns observed, it is important to look at OC results for comparison. In doing so, it can be seen that within treatment groups the magnitude of the OC response is greater than the magnitude of the LOCF response (see efficacy tables for the individual studies). Figure 3 as compared to Figure 2 illustrates this point. The magnitude of the OC responses for both the paroxetine and imipramine groups in the positive and supportive studies (03-001, 03-004, 03-005 and 03-006) are notably larger than what was seen for the LOCF results. Note that the placebo responses from the OC and LOCF analyses are not appreciably different. These differences between the LOCF and OC responses are not surprising since patients showing improvement may be expected to stay on trial longer, however it does make it difficult to assess the size of the true treatment effect.

6. For all 11 studies, the patient-rated scales showed no efficacy or minimal efficacy. According to the medical reviewer and references provided by the sponsor, these scales have been shown to provide unreliable estimates of symptoms of depression, therefore there is little reason to be concerned about the lack of efficacy.

7. The results of the fixed dose study (PAR 09) suggested that a 20 mg dose of paroxetine was superior to 10 mg , 30 mg and 40 mg, however, the results from the efficacy studies where patients were titrated to their "best" dose showed that a higher dose was needed to show efficacy. The mean daily dose in the PAR 01, 02 and 03 studies was about 30 mg/day while the maximum dose was about 38 mg/day (this was, also, the average dose recommended by investigators).

The mean daily dose of paroxetine in mg/kg ranged from .37 to .44 and the maximum dose ranged from .47 to .57 mg/kg in the 11 USA efficacy studies.

Compliance was high in all treatment groups in all 11 studies. In the paroxetine group compliance ranged from %.

In conclusion, the results from the 11 USA studies provide sufficient statistical evidence of the effectiveness of paroxetine for the treatment of depression.

Joy D. Mele

Joy D. Mele, M.S.
Mathematical Statistician

Concur: Dr. Nevius SEN 9-9-92

Dr. Dubey 9-11-92

cc:
Orig. NDA 20-031
HFD-120
HFD-120/Drs. Leber, Laughren
HFD-120/Mr. David
HFD-713/Dr. Dubey [File: DRU 1.3.2]
HFD-713/Group 2 File
HFD-713/Ms. Mele
HFD-344/Dr. Lisook
Chron.

Mele/x2814/SERB/WordPerfect-paxil.rev/September 2, 1992

This review consists of 25 pages of text and tables with 1 additional table and 3 figures attached.

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Clinical Alerts
ClinicalTrials.gov
PubMed Central

1: Fava M, Amsterdam JD, Deltito JA, Salzman C, Schwaller M, Dunner DL. Related Articles, Links

A double-blind study of paroxetine, fluoxetine, and placebo in outpatients with major depression.
Ann Clin Psychiatry. 1998 Dec;10(4):145-50.
PMID: 9988054 [PubMed - indexed for MEDLINE]

2: Cohn JB, Wilcox CS. Related Articles, Links

Paroxetine in major depression: a double-blind trial with imipramine and placebo.
J Clin Psychiatry. 1992 Feb;53 Suppl:52-6.
PMID: 1531826 [PubMed - indexed for MEDLINE]

3: Shrivastava RK, Shrivastava SH, Overweg N, Blumhardt CL. Related Articles, Links

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J Clin Psychiatry. 1992 Feb;53 Suppl:48-51.
PMID: 1531825 [PubMed - indexed for MEDLINE]

4: Feighner JP, Boyer WF. Related Articles, Links

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J Clin Psychiatry. 1992 Feb;53 Suppl:44-7.
PMID: 1531824 [PubMed - indexed for MEDLINE]

5: Smith WT, Glaudin V. Related Articles, Links

A placebo-controlled trial of paroxetine in the treatment of major depression.
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PMID: 1531822 [PubMed - indexed for MEDLINE]

6: Rickels K, Amsterdam J, Clary C, Fox I, Schweizer E, Weise C. Related Articles, Links

The efficacy and safety of paroxetine compared with placebo in outpatients with major depression.
J Clin Psychiatry. 1992 Feb;53 Suppl:30-2.
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Paroxetine in the treatment of depression: a comparison with imipramine and placebo.
Acta Psychiatr Scand Suppl. 1989;350:125-9.
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Result 1.

Accession Number	CN-00088476
Author	Feighner JP
Institution	Feighner Research Institute, San Diego, California.
Title	A double-blind comparison of paroxetine, imipramine and placebo in depressed outpatients.
Source	International clinical psychopharmacology. Vol.6 Suppl 4, pp.31-5, 1992 Jun.
Abstract	Diagnostic criteria, random parallel placebo-controlled study design, and appropriate clinical assessment for both safety and efficacy are all among the essential requirements for the evaluation of a new antidepressant agent. Paroxetine and imipramine were compared for efficacy and safety in a large multicentre, randomized, placebo-controlled, double-blind, parallel design study in the USA. The study involved 717 outpatients with major depressive disorder; after a one-week washout period they were treated for 6 weeks, being assessed at weekly intervals. The results from all six participant centres combined showed that both active drugs were statistically superior to placebo by week 2 and that the antidepressant response was significant for both. Paroxetine was better tolerated than imipramine with fewer dropouts from side effects. This combined study clearly indicated that paroxetine was an effective and well-tolerated antidepressant.

Result 2.

Accession Number	CN-00090268
Author	Claghorn JL, Kiev A, Rickels K, Smith WT, Dunbar GC
Institution	Clinical Research Associates, Houston, Tex.
Title	Paroxetine versus placebo: a double-blind comparison in depressed patients.
Source	The Journal of clinical psychiatry. 53(12):434-8, 1992 Dec.
Abstract	**BACKGROUND:** Paroxetine is a potent and selective serotonin reuptake inhibitor (SSRI). The present study assessed the efficacy and tolerability of paroxetine against placebo in depressed outpatients. **METHOD:** A double-blind, parallel-group study was undertaken in four stand-alone centers. Patients aged 18-65 years, meeting DSM-III criteria for major depression, and having a Hamilton Rating Scale for Depression (HAM-D) score > or = 18 on the first 17 items of the HAM-D-21 were randomized to paroxetine or placebo for 6 weeks of treatment. Efficacy outcome variables included the HAM-D, the Montgomery-Asberg Depression Rating Scale, the Clinical Global Impressions Scale (CGI), and the Covi Anxiety Scale. Tolerability was assessed by asking a non-leading question. Routine laboratory safety and vital sign data from all four centers were pooled. The primary analysis used the intention-to-treat sample and for efficacy variables the last-observation-carried-forward data set was employed. Statistical methods included one-way analysis of variance for parametric and Fisher exact test for nonparametric variables. **RESULTS:** Significant differences (p < or = .05) were found between paroxetine and placebo on the HAM-D and CGI by Week 2 and on all efficacy outcome variables by Week 4. Improvement on the

HAM-D sleep factor occurred 2 weeks prior to that seen on the retardation factor. Similar results were obtained when an adequate treatment group (therapy for > or = 28 days) was considered. A full clinical response (CGI-severity of illness score 1 or 2) was seen in over 40% of subjects. Adverse events were more common for paroxetine compared with placebo (p < or = .01). Somnolence was twice more common than nervousness. Dropout due to adverse events was similar between therapies. Paroxetine had no clinically significant effect on laboratory safety data or vital signs. **CONCLUSION:** Paroxetine was an effective, well tolerated, and safe antidepressant. Side effects were typical of the SSRI class of drugs. Symptoms indicative of a nonalerting profile were more common than those associated with alerting effects.

Result 3.

Accession Number	CN-00082174
Author	Kiev A
Institution	Social Psychiatry Research Institute, Inc., New York, N.Y. 10021.
Title	A double-blind, placebo-controlled study of paroxetine in depressed outpatients.
Source	The Journal of clinical psychiatry. Vol.53 Suppl, pp.27-9, 1992 Feb.
Abstract	Paroxetine is an investigational antidepressant that acts through selective inhibition of serotonin reuptake at the synapse. In this study, 81 outpatients with major depression according to DSM-III criteria were treated with either paroxetine or placebo in a 6-week, randomized, double-blind study. Paroxetine was significantly superior to placebo on all major efficacy variables, including depression as well as anxiety, cognitive disturbance, insomnia, psychomotor retardation, and sleep disturbance. Significant differences in favor of paroxetine were apparent by Week 2. Paroxetine was also well tolerated. The results support the efficacy and safety of paroxetine as a treatment for patients with major depression.

Result 4.

Accession Number	CN-00082175
Author	Rickels K, Amsterdam J, Clary C, Fox I, Schweizer E, Weise C
Institution	Department of Psychiatry, University of Pennsylvania, Philadelphia 19104.
Title	The efficacy and safety of paroxetine compared with placebo in outpatients with major depression.
Source	The Journal of clinical psychiatry. Vol.53 Suppl, pp.30-2, 1992 Feb.
Abstract	Paroxetine, a phenylpiperidine derivative, is an antidepressant that selectively inhibits serotonin reuptake. In this study 111 outpatients with major depression diagnosed by DSM-III criteria were treated with either paroxetine or placebo in a 6-week, randomized, double-blind study. Paroxetine was significantly superior to placebo on six of the seven major efficacy variables. Significant differences in favor of paroxetine were apparent by Week 2. Paroxetine was also well tolerated. These results support the efficacy and safety of paroxetine as a treatment for patients with major depression.

Result 5.

Accession Number	CN-00082176
Author	Claghorn JL

Institution	Clinical Research Associates, Houston, TX 77098.
Title	The safety and efficacy of paroxetine compared with placebo in a double-blind trial of depressed outpatients.
Source	The Journal of clinical psychiatry. Vol.53 Suppl, pp.33-5, 1992 Feb.
Abstract	Considerable research shows that serotonin dysfunction is implicated in major depression. Paroxetine is an investigational antidepressant that appears to act by selectively blocking neuronal serotonin uptake. Seventy-two outpatients with moderate-to-severe major depression entered this 6-week, double-blind comparison of paroxetine and placebo. The results showed clear and significant superiority of paroxetine on all of the major outcome variables. These included physician-rated measures such as the Hamilton Rating Scale for Depression and its four factor scores, the Clinical Global Impressions scale, the Montgomery and Asberg Depression Rating Scale, and the Raskin Depression Scale. Results on these agreed well with patient-rated measures like the Hopkins Symptom Checklist and Patient Global Evaluation Scale. Paroxetine was also very well tolerated. Nausea and constipation occurred significantly more often with paroxetine, but only 9% of paroxetine patients dropped out of the study due either in whole or in part to an adverse effect. This compares to 8% of the placebo patients who were discontinued for the same reason. This study suggests that paroxetine is a safe and effective medication for the treatment of major depression.

Result 6.

Accession Number	CN-00082177
Author	Smith WT, Glaudin V
Institution	Pacific Northwest Clinical Research Center, Portland, OR 97232.
Title	A placebo-controlled trial of paroxetine in the treatment of major depression.
Source	The Journal of clinical psychiatry. Vol.53 Suppl, pp.36-9, 1992 Feb.
Abstract	Paroxetine is a phenylpiperidine compound that selectively inhibits neuronal serotonin uptake in man. In this study, the efficacy of paroxetine was compared with that of placebo in the treatment of 66 outpatients with the diagnosis of moderate-to-severe major depression. The research was a 6-week, prospective, double-blind design after a 1-week placebo baseline phase. Paroxetine was associated with a consistent pattern of greater improvement on the primary efficacy scales, but the differences were not statistically significant. Paroxetine did produce significantly greater improvement than placebo for patients whose illness had lasted more than 1 year, and there was a significant reduction in suicidal ideation. Significantly fewer dropouts were due to lack of efficacy in those patients treated with paroxetine compared with those in the placebo group. Paroxetine was well tolerated. There was no difference between paroxetine and placebo in the rate of adverse effects or in the number of patients who dropped out because of adverse effects.

Result 7.

Accession Number	CN-00082178
Author	Fabre LF
Institution	Fabre Clinic, Houston, TX 77004.
Title	A 6-week, double-blind trial of paroxetine, imipramine, and placebo in depressed outpatients.
Source	The Journal of clinical psychiatry. Vol.53 Suppl, pp.40-3, 1992 Feb.

Abstract Paroxetine is a novel antidepressant that selectively inhibits neuronal reuptake of serotonin. Results are reported from a 6-week, double-blind trial of paroxetine, imipramine, and placebo in 120 outpatients with DSM-III major depression. Paroxetine was significantly superior to placebo on almost all measures. This included the main outcome variable, the Hamilton Rating Scale for Depression (HAM-D), and its factor scores, anxiety-somatization, cognitive disturbance, psychomotor retardation, and sleep disturbance. There were no significant differences between paroxetine and imipramine on the same scales. Imipramine-treated patients were significantly more likely than those taking placebo to report one or more adverse effects, which were predominantly anticholinergic in nature. There was no significant difference in the number of paroxetine and placebo patients who reported one or more adverse effects. The results of this and similar studies indicate that paroxetine is an effective treatment in major depression and has a favorable side effect profile.

Result 8.

Accession Number CN-00082179

Author Feighner JP, Boyer WF

Institution Feighner Research Institute, La Mesa, Calif.

Title Paroxetine in the treatment of depression: a comparison with imipramine and placebo.

Source The Journal of clinical psychiatry. Vol.53 Suppl, pp.44-7, 1992 Feb.

Abstract Paroxetine is a selective serotonin reuptake inhibitor with significant antidepressant properties. This was a 6-week placebo- and imipramine-controlled study of 120 outpatients with major depression. Paroxetine was statistically significantly superior to placebo on almost all outcome measures. This was apparent as early as 1 week. Paroxetine was also significantly superior to imipramine on the Hamilton Rating Scale for Depression total score. Paroxetine was generally better tolerated than imipramine. These results strongly support paroxetine's effectiveness in the treatment of major depression and suggest that paroxetine will be a valuable addition to the options in treating depressive illness.

Result 9.

Accession Number CN-00082180

Author Shrivastava RK, Shrivastava SH, Overweg N, Blumhardt CL

Institution Eastside Comprehensive Medical Services, New York, N.Y.

Title A double-blind comparison of paroxetine, imipramine, and placebo in major depression.

Source The Journal of clinical psychiatry. Vol.53 Suppl, pp.48-51, 1992 Feb.

Abstract Results from a single-center, 6-week, double-blind, randomized prospective study of paroxetine, a selective serotonin reuptake inhibitor; imipramine; and placebo are reported. One hundred twenty outpatients with a moderate-to-severe DSM-III diagnosis of major depression were randomly assigned to one of the three treatments following a 4- to 10-day single-blind placebo washout period. Significant differences favoring paroxetine over placebo were present at endpoint on most major efficacy measures. Paroxetine was also well tolerated; 5 (15%) paroxetine and 5 (14%) placebo patients dropped out of the study due to adverse effects. Imipramine, however, was comparatively poorly tolerated. Forty-five percent of imipramine-treated patients (N = 17) dropped out of the study due to adverse effects. None of the efficacy measures showed a significant difference between imipramine and

placebo. This finding was probably due to the high number of imipramine patients who discontinued before they could improve. These results support the efficacy of paroxetine in the treatment of major depression and underline its favorable side effect profile compared with tricyclic antidepressants.

Record 10.

Accession Number	CN-00082181
Author	Cohn JB, Wilcox CS
Institution	Pharmacology Research Institute, Long Beach, CA 90807-0289.
Title	Paroxetine in major depression: a double-blind trial with imipramine and placebo.
Source	The Journal of clinical psychiatry. Vol.53 Suppl, pp.52-6, 1992 Feb.
Abstract	Paroxetine is a selective serotonin reuptake inhibitor which is being developed as an antidepressant. Previous studies suggest it is effective in the treatment of depression and has a low incidence of side effects. The authors report on a 6-week, randomized, prospective trial of paroxetine, imipramine, and placebo in 120 outpatients with major depression. The results showed that paroxetine was significantly superior to placebo in relieving depression. There were no significant differences in antidepressant efficacy between paroxetine and imipramine. However, paroxetine was also significantly superior to placebo on several measures of anxiety. Imipramine either was not superior on these measures or took longer to show a significant difference. Paroxetine lacked the typical anticholinergic side effects that accompanied imipramine therapy. The results show that paroxetine is an effective antidepressant that may have value especially when depression is accompanied by significant anxiety.