CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:020936

STATISTICAL REVIEW(S)

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Date:

Statistical Review and Evaluation

JUN 18 1998

NDA #: 20-936

Applicant: SmithKline Beecham

Name of the Drug: Paxil® CR (paroxetine hydrochloride) Tablets

Indication: Depression

Documents Reviewed: Volumes 1.1 to 1.3, 1.55 to 1.76 submitted Dec.19, 1997, Vols. 5.1 to 5.9 submitted April 21, 1998, amendments dated Jan.26, 1998; Feb.10, 1998; May 4, 1998

Clinical Reviewer: Gregory Dubitsky, M.D.(HFD-120)

The issues in this review have been discussed with the reviewing medical officer, Gregory Dubitsky, M.D.(HFD-120).

Various Sections of this review are:

I. Background/Introduction

Paxil (immediate release (IR)) is an approved drug (NDA 20-031 and NDA 20-710). The efficacy data in this NDA for controlled-release (CR) formulation for the treatment of depression are provided by two double-blind, randomized, parallel group, placebo controlled, flexible dose studies 448 and 449. This formulation is not marketed in any country nor has it been reviewed by any other regulatory agency. Later, on April 21, 1998, the final report of Study 29060/487 in elderly patients with depression has been submitted.

One study (449) was conducted in the US and Canada, one (448) in

the US alone. In these trials, non-elderly adult patients with major depressive disorder were treated for 12 weeks double-blind, after a one-week placebo run-in phase. Paxil IR served as an active comparator. A total of 648 patients - 216 for CR, 219 for IR, and 213 for placebo - were randomized in these two studies. In both studies, patients began treatment at the lowest dosage (CR=25mg once daily; IR=20mg once daily) and titrated upward to Investigator determined effectiveness. The maximum dosage permitted for Paxil CR was 62.5mg once daily while that for Paxil IR was 50mg once daily.

Three hundred nineteen patients in three treatment arms comprised the ITT population in Study 487, conducted in 31 sites in North America. This study in elderly patients is similar to the above studies, except that the doses were lower.

Summary design aspects of Studies 448 and 449 are attached as Table 0.1.1.[1]

II. Clinical Studies

All analyses referred to in this report are the sponsor's analyses, except where specifically mentioned to be done by this reviewer.

This reviewer consulted Dr. Dubitsky (HFD-120) regarding the most important efficacy variables. They are "Change from Baseline in HAM-D Total", "Change from Baseline in HAM-D Depressed Mood Item", and "Change from Baseline in CGI Severity of Illness".

1. Study 448

Study 448 was a randomized, 12-week double-blind, placebo-controlled, flexible-dose (25 to 62.5 mg/day Paxil CR and 20 to 50 mg/day Paxil IR), twenty-center U.S. study consisting of a 1-week, single-blind, placebo run-in period, in outpatients (180 enrolled and 169 ITT patients) with major depression or bipolar disorder, depressed.

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[1] In the Table (or Appendix or Figure; no separate numbering systems have been created for these) number i.j.k, i stands for the serial number of the study in the list of studies above (except that 0 indicates overall or "common to all"), j stands for the Section or Group number for the tables in a particular study, and k stands for the Table number in that Section.

1A. Objective

The primary objective of this study was to demonstrate the efficacy of modified release paroxetine in the treatment of major depression.

The secondary objective was to compare, through descriptive listings, the tolerability of modified release paroxetine with the immediate release formulation.

1B. Disposition of Patients

Five of the 315 patients randomized to double-blind study medication, were not included in the intent-to-treat (ITT) population because they withdrew on the first day following randomization and became lost to follow-up (Paxil Cr: 2; Paxil IR: 1; Placebo: 2).

The percentages of patients remaining in study by week is presented in Table and Figure 1.1.1. These percentages at (the last) Visit 12 were 69.2%, 66.7%, and 73.3%, respectively, for the Paxil CR, Paxil IR, and placebo groups. At Visit 4, the respective percentages were 81%, 76%, and 90%.

Patients withdrew due to adverse experiences twice as frequently in the IR (14%) and CR (13%) Paxil groups as in the placebo (6%) group. More patients withdrew due to lack of efficacy in the placebo group (9.9%) than in the Paxil groups (CR, 2.9%; IR, 5.7%).

In the Paxil groups, most of the withdrawals due to adverse experiences occurred in the first week; whereas, in the placebo group, those occurred towards Week 8 and later.

1C. Comparability of Treatment Groups

In the three treatment groups Paxil CR, Paxil IR, and placebo, respectively, the percentages of females were 60%, 64%, and 66%; the percentages of whites were 91%, 90%, and 85%. The mean age was around 39 years in each of the three groups. The mean weight in the Paxil CR group was 180 lb (about 12 lbs more than that in the other two groups).

The sponsor stated (p.9, Vol.1.60), "...there was no statistically significant difference between the patient groups on each treatment across the different age groups, different CGI

categories, patients of different race, and no statistically significant difference in the treatments given to the males and females."

The sponsor also stated that there were no statistically significant differences between the different treatment groups with respect to HAMD total, Depressed mood item, Anxiety factor, Sleep disturbance, Physical health, Subjective feeling, Leisure Time activities, Social relationship and General activities scores.

However, the p-values were not provided.

1D. Efficacy Results (Sponsor's Analyses)

HAMD Total was the protocol-mentioned primary efficacy variable.

The protocol stated, "The change from baseline to study endpoint in the CGI severity of illness item and HAMD depressed mood item will be analyzed using the Wilcoxon rank sum test. No adjustment will be made for center or covariates." However, the NDA provided results for HAMD depessed moood item (as well as for HAMD total, as stated) adjusting for the effect of "Center Group Only" in one analysis and of "Center group, age, sex, baseline value, and duration of current episode of depression" in another analysis.

Although the sponsor stated that these covariates were prospectively defined (may be in their internal document), this reviewer does not see them specifically cited in the protocol. The protocol stated, "The effect of suitable covariates will also be investigated e.g. baseline scores and demographic parameters." This reviewer's 1-way analyses without any covariates did not change the overall picture with respect to statistical significance.

The (1) Results with mean differences, 95% confidence intervals, and p-values (OC and LOCF) and (2) Graphs for cumulative distribution functions, for (adjusted) Mean Changes From Baseline are attached as Tables 1.3.1, 1.3.2, and Figure 1.3.3 (HAM-D Total); 1.4.1, 1.4.2, and 1.4.3 (HAM-D Depressed Mood Item), 1.5.1, 1.5.2, and 1.5.3 (CGI Severity of Illness).

The all-centers-combined results provided statistically clearly significant results in favor of Paxil CR. However, there was a

statistically significant treatment by center interaction. The sponsor stated, "Therefore, the results from Study 448 need to be interpreted with some caution."

When the results from the center group 002/004 were removed from the analysis, the treatment by center interaction was non-significant and the difference between paroxetine CR and placebo was, generally, not statistically significant with respect to HAMD total (attached Tables 1.3.1(b) and 1.3.2(b)) and CGI Severity of Illness (Tables 1.4.1(b) and 1.4.2(b)), although Paxil CR was numerically superior to placebo.

The sponsor stated that this effect was produced mainly by the 18 patients in ceter 002. In this reviewer's language, the statistical significance of the all-centers-combined results were driven by this center. Excluding this center group, the numerical differences beween Paxil CR and placebo are much smaller in this study than those in the next Study 449. Even the shift in the numerical differences when 002/004 center group was included versus not included was so remarkable.

Generally, we see that even the placebo patients get better over time. The sponsor stated that relatively more patients in this center (002) were severely ill; those who received active treatment improved a lot and those who received placebo deteriorated. Thus this center provided outstandingly strong results in favor of the active treatment. Results for the center group 002/004 are attached as Table 1.3.4 for HAMD Total (as a sample).

This reviewer noted that there were relatively more patients in the 001/020 center group also, who were severely ill at baseline. This reviewer's analyses showed that the Placebo group in this center group had a -18.0 (improvement) HAM-D Total mean Change from baseline at Week 12 instead of +6.1 (deterioration) for placebo in the 002/004 center group. In particular, the placebo patients in Center 001, who were severely ill at baseline improved a lot (-30, -17) at Week 8 and Week 12 (-20).

Overall, this study provided numerical evidence in favor of the efficacy of Paxil CR. The statistically significant evidence with respect HAMD Depressed Mood Item is beyond this 002/004 center group controversy. Even by excluding the 002/004 center group, there was statistical evidence in favor of the efficacy of Paxil CR with respect to HAMD Depressed Mood Item. With respect to the other two efficacy variables, there were only occassionally statistically significant results, by excluding the 002/004 center group. Moreover, the results for Paxil CR were

numerically stronger than those for Paxil IR. The sponsor stated (vol.1.68, p.143), "Again, this difference can be explained by the considerably greater proportion of patients withdrawing from the study in the paroxetine IR group." From the disposition of patients, this reviewer sees only a negligible difference (<3%) between CR and IR patients remaining in the study at Week 12; the corresponding difference at Week 6 was 8.4%.

This reviewer's review of individual patient data and 'alternative analyses excluding Center 002' are only supportive of the sponsor's analyses and comments. The p-values for Paxil CR or IR vs placebo within Center 002 (done by this reviewer) were highly significant, even with only 5 or 6 patients in each arm. We may recall that there were twenty centers with 169 ITT patients.

1E. <u>Reviewer's Comments and Conclusions on Study 448</u>

This study provided, at least, some numerical evidence in favor of the efficacy of Paxil CR. The sponsor stated (vol. 1.68, p.142), "Despite this treatment-by-center interaction, however, results of Study 448 were supportive of the findings of Study 449."

Except for the statistically significant treatment by center interaction, the all-centers-combined results of this study provided statistically clearly significant results in favor of the efficacy of Paxil CR.

The statistically strong significance of the all-centers-combined results were driven by one center. Excluding this center (analyses by this reviewer) or center group 002/004 (by sponsor), the statistical significance was only sporadic and the numerical differences beween Paxil CR and placebo were much smaller (still in favor of Paxil CR) in this study than those in the next Study 449. Even the shift in the numerical differences when 002/004 center group was included versus not included was so remarkable.

The statistically significant evidence with respect to HAMD Depressed Mood Item is beyond this interaction controversy. Even by excluding the 002/004 center group, there was statistical evidence in favor of the efficacy of Paxil CR with respect to HAMD Depressed Mood Item. With respect to the other two efficacy variables, there were occassionally significant results when the 002/004 center group or center 002 was excluded. Moreover, the results for Paxil CR were numerically stronger than those for Paxil IR.

From the graphs for change from baseline for the dropout cohorts (Stat. Vol. 1.60, pages 74 to 76; not attached to this report), we see that the placebo group almost always performed no better than Paxil CR group. Therefore, there should not be a concern that the drug superiority might have been shown by dropping out of well-responding placebo patients.

2. Study 449

Study 449 was a randomized, 12-week double-blind, placebo-controlled, flexible-dose (25 to 62.5 mg/day Paxil CR and 20 to 50 mg/day Paxil IR), twenty-center U.S./Canada study consisting of a 1-week, single-blind, placebo run-in period, in outpatients (429 screened, 333 randomized, and 330 ITT patients) with major depression.

2A. Objective

The primary objective of this study was to demonstrate the efficacy of modified release paroxetine in the treatment of major depression.

The secondary objective was to compare, through descriptive listings, the tolerability of modified release paroxetine with the immediate release formulation.

2B. Disposition of Patients

Three of the 333 patients randomized to double-blind study medication, were not included in the intent-to-treat (ITT) population because they withdrew on the first day following randomization and became lost to follow-up (Paxil Cr: 2; Paxil IR: 1).

The percentages of patients remaining in study by week is presented in Table and Figure 2.1.1. These percentages at (the last) Visit Week 12 were 75.0%, 67.0%, and 70.0%, respectively, for the Paxil CR, Paxil IR, and placebo groups. At Visit Week 4, the respective percentages were 87%, 80%, and 86%.

Patients withdrew due to adverse experiences twice as frequently in the IR (16%) group as in the CR (8.3%) group (in the placebo group 5.5%). More patients withdrew due to lack of efficacy in

the placebo group (8.2%) than in the Paxil groups (CR, 2.8%; IR, 1.8%). Overall, there were more early withdrawals from the IR group than in the other groups.

2C. Comparability of Treatment Groups

In the three treatment groups Paxil CR, Paxil IR, and placebo, respectively, the percentages of females were 67%, 74%, and 60%; the percentages of whites were 85%, 84%, and 85%. The mean age was around 41 years in Paxil IR and placebo groups and 42 in the Paxil CR group. The mean weight in the Paxil CR, IR and placebo group was, respectively, 178 Lb, 175 Lb, and 173 Lb.

The sponsor stated on pages 170-71 of Vol.1.65 that there was no statistically significant difference between the patient groups on demographic and baseline variables except on HAMD Sleep factor. The differences in the sleep factor scores were not considered to be clinically meaningful.

However, the p-values were not provided.

2D. Efficacy Results (Sponsor's Analyses)

HAMD Total was the protocol-mentioned primary efficacy variable.

The protocol stated, "The change from baseline to study endpoint in the CGI severity of illness item and HAMD depressed mood item will be analyzed using the Wilcoxon rank sum test. No adjustment will be made for center or covariates." However, the NDA provided results for HAMD depessed moood item (as well as for HAMD total, as stated) adjusting for the effect of "Center Group Only" in one analysis and of "Center group, age, sex, baseline value, and duration of current episode of depression" in another analysis.

Although the sponsor stated that these covariates were prospectively defined (may be in their internal document), this reviewer does not see them specifically cited in the protocol. The protocol stated, "The effect of suitable covariates will also be investigated e.g. baseline scores and demographic parameters." This reviewer's analyses without any covariates did not change the overall picture with respect to statistical significance.

The (1) Results with mean differences, 95% confidence intervals, and p-values (OC and LOCF) and (2) Graphs for cumulative

distribution functions, for (adjusted) Mean Changes From Baseline are attached as Tables 2.3.1, 2.3.2, and Figure 2.3.3 (HAM-D Total); 2.4.1, 2.4.2, and 2.4.3 (HAM-D Depressed Mood Item), 2.5.1, 2.5.2, and 2.5.3 (CGI Severity of Illness).

All the results were similar whether the data from Center 017 (DR. Robert Fiddes) were included or not. For CGI Severity of Illness, OC results at Week 12 were not statistically significant. Other than that, all the results from Week 6 and after, with respect to the efficacy variables mentioned, were clearly in favor of the efficacy of Paxil CR. Paxil IR results were reasonably acceptable only with respect to HAMD Depressed Mood Item. With respect HAMD Total and CGI Severity of Illness, Paxil IR results were only infrequently statistically significant.

This reviewer's alternative analyses, excluding Center 017, showed the efficacy of Paxil CR starting from Week 6; there were no significant p-values up to Week 4.

2E. Reviewer's Comments and Conclusions on Study 449

This study provided statistically significant evidence in favor of the efficacy of Paxil CR starting from Week 6.

From the graphs for change from baseline for the dropout cohorts (Stat. Vol. 1.65, pages 000210 to 000212; not attached to this report), we see that dropouts from the placebo group almost always performed worse than Paxil CR group. Week 1 dropouts are not important because of very small improvements anyway, in all treatment arms. At Week 4, dropouts from the placebo group had slightly better results than those from the Paxil CR group. However, compared with the much bigger improvements produced by much bigger number of dropouts after Week 4 among the Paxil dropouts (compared with placebo dropouts), superiority of placebo dropouts at Week 4 should not be of concern overall. That is, there should not be a concern that the drug superiority might have been shown by dropping out of well-responding placebo patients.

3. Study 487 (Elderly Patients)

Study 487 was a randomized, 12-week double-blind treatment phase,

placebo-controlled, flexible-dose (12.5 to 50 mg/day Paxil CR and 10 to 40 mg/day Paxil IR), thirty-center North America study consisting of a 1-week, single-blind, placebo run-in period, in elderly patients (396 screened, 323 randomized, and 319 ITT patients) with major depression.

3A. Objective

The primary objective of this study was to demonstrate the efficacy of modified release paroxetine in the treatment of major depression in elderly patients.

The secondary objective was to compare, through descriptive listings, the tolerability of modified release paroxetine with the immediate release formulation.

3B. Disposition of Patients

Four of the 323 patients randomized to double-blind study medication, were not included in the intent-to-treat (ITT) population because they did not yield an on-drug safety or efficacy assessment (Paxil Cr: 2; Paxil IR: 2).

The percentages of patients remaining in the study by week is presented in Table and Figure 3.1.1. These percentages at (the last) Visit Week 12 were 77.9%, 72.6%, and 77.1%, respectively, for the Paxil CR, Paxil IR, and placebo groups. At Visit Week 4, the respective percentages were 87%, 85%, and 89%.

Patients withdrew due to adverse experiences twice as frequently in the IR (16%) group and 1.5 times as fruquently in the CR group (13%) as in the placebo group (8.3%).

3C. Comparability of Treatment Groups

In the three treatment groups Paxil CR, Paxil IR, and placebo, respectively, the percentages of females were 44%, 57%, and 58%; the percentages of whites were 96%, 95%, and 95%. The mean age was around 70 years in Paxil CR and IR groups and 69 in the Placebo group. The mean weight in the Paxil CR, IR and placebo group was, respectively, 175 Lb, 173 Lb, and 170 Lb.

No statistically significant difference between the patient groups on demographic and baseline variables was seen. The sponsor also stated so. However, the p-values were not provided.

Table 1.3.1 (b)

Baseline and Change from Baseline in HAMD Total Score
Excluding ~~Centre Group~~ 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)	p-value		Mean (95% C.I.)	p-value	
Baseline	22.9	(0.26)	94	23.3	(0.28)	96	23.2	(0.29)	93						
Week 1	-3.9	(0.41)	92	-3.6	(0.42)	95	-3.2	(0.41)	92	-0.6 (-1.77, 0.48)	0.258		-0.4 (-1.51, 0.73)	0.496	
Week 2	-7.3	(0.55)	80	-6.5	(0.56)	77	-6.3	(0.52)	89	-1.0 (-2.43, 0.47)	0.184		-0.1 (-1.62, 1.35)	0.855	
Week 3	-9.6	(0.65)	79	-7.4	(0.66)	79	-7.9	(0.63)	84	-1.7 (-3.45, 0.03)	0.055		0.5 (-1.31, 2.22)	0.613	
Week 4	-11.0	(0.73)	78	-9.3	(0.76)	75	-9.8	(0.69)	86	-1.2 (-3.20, 0.70)	0.208		0.5 (-1.51, 2.48)	0.635	
Week 6	-12.0	(0.73)	71	-11.6	(0.76)	70	-9.6	(0.70)	79	-2.4 (-4.41, -0.47)	0.015		-2.0 (-4.01, -0.04)	0.045	
Week 8	-13.8	(0.71)	72	-13.7	(0.78)	62	-11.6	(0.70)	74	-2.2 (-4.13, -0.26)	0.026		-2.1 (-4.14, -0.06)	0.044	
Week 12	-14.4	(0.86)	58	-14.2	(0.96)	50	-12.4	(0.84)	61	-1.9 (-4.27, 0.45)	0.111		-1.8 (-4.23, 0.73)	0.164	
70% End Point	-10.7	(0.70)	94	-9.2	(0.71)	96	-9.1	(0.71)	93	-1.6 (-3.51, 0.33)	0.105		-0.1 (-2.04, 1.82)	0.911	
Wk 12 End Point	-12.0	(0.81)	94	-10.7	(0.82)	96	-10.7	(0.81)	93	-1.3 (-3.50, 0.93)	0.254		0.1 (-2.14, 2.30)	0.941	

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1W_NEW.SAS (25AUG97 15:12)

Table 1.3.2 (a)

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)	p-value		Mean (95% C.I.)	p-value	
seline	23.0	(0.26)	102	23.3	(0.28)	104	23.4	(0.29)	101						
ek 2 LOCF	-6.8	(0.49)	102	-6.0	(0.50)	104	-5.8	(0.49)	101	-1.0 (-2.31, 0.38)	0.159		-0.1 (-1.48, 1.21)	0.843	
ek 4 LOCF	-10.3	(0.67)	102	-8.7	(0.68)	104	-9.1	(0.68)	101	-1.2 (-3.04, 0.63)	0.198		0.4 (-1.40, 2.28)	0.641	
ek 6 LOCF	-11.2	(0.69)	102	-9.9	(0.70)	104	-8.7	(0.69)	101	-2.4 (-4.30, -0.53)	0.012		-1.2 (-3.07, 0.71)	0.220	
ek 8 LOCF	-12.3	(0.73)	102	-10.6	(0.75)	104	-9.9	(0.74)	101	-2.4 (-4.37, -0.36)	0.021		-0.7 (-2.69, 1.34)	0.511	
ek 12 LOCF	-12.7	(0.80)	102	-11.1	(0.81)	104	-9.9	(0.80)	101	-2.8 (-4.94, -0.59)	0.013		-1.2 (-3.40, 0.97)	0.275	

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LOCF14_1.SAS (04SEP97 13:46)

Table 1.3.2 (b)

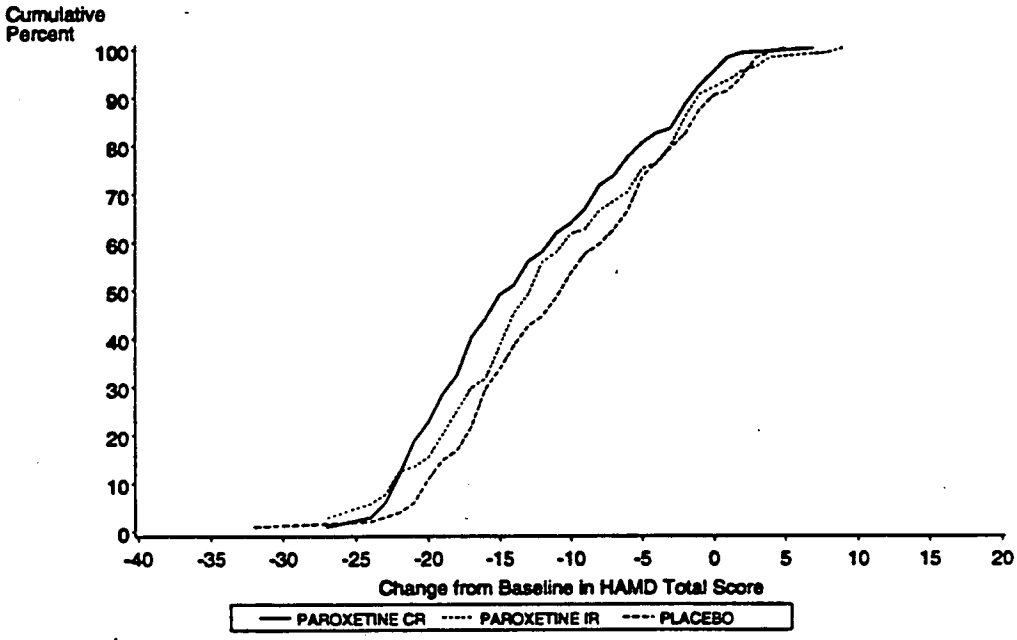
Baseline and Change from Baseline in HAMD Total Score
Excluding Centre Group 002/004
ing for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)	p-value		Mean (95% C.I.)	p-value	
	22.9	(0.26)	94	23.3	(0.28)	96	23.2	(0.29)	93						
	-6.6	(0.51)	94	-6.0	(0.52)	96	-6.3	(0.51)	93	-0.3 (-1.66, 1.12)	0.700		0.3 (-1.09, 1.70)	0.667	
	-9.8	(0.69)	94	-8.1	(0.70)	96	-9.4	(0.70)	93	-0.4 (-2.31, 1.47)	0.660		1.3 (-0.58, 3.21)	0.173	
	-10.6	(0.71)	94	-9.4	(0.72)	96	-9.0	(0.71)	93	-1.6 (-3.53, 0.32)	0.103		-0.4 (-2.36, 1.51)	0.665	
	-11.7	(0.75)	94	-10.0	(0.76)	96	-10.3	(0.76)	93	-1.4 (-3.50, 0.62)	0.170		0.3 (-1.82, 2.32)	0.810	
F	-12.0	(0.81)	94	-10.7	(0.82)	96	-10.7	(0.81)	93	-1.3 (-3.50, 0.93)	0.254		0.1 (-2.14, 2.30)	0.941	

Note: Only patients with a baseline and at least one post baseline assessment

8.2 Cumulative Frequency Distribution Plots

Paroxetine CR - Protocol : 448
Figure 1.3.3
Cumulative Frequency Distribution
HAMD Total Score
Change from Baseline at Endpoint



1.3.3

Figure presents the cumulative frequency distribution of the change from baseline in HAMD total score. Paroxetine CR patients had the highest gradient, with placebo the least steep of the three. All three cumulative frequency distributions were reasonably linear between -25 and 0, the gradients were much lower before/after these points . Figure 14.4.18.1 is similar to above, but this plots change from baseline in mood item score only. Much the same trend is shown in this figure. Figure 14.6.1.1 shows the cumulative frequency distribution of the change from baseline in CGI Severity score. Again there is some suggestion of a difference between paroxetine CR and placebo, but less so between paroxetine IR and placebo.

Table 1.3.4

Baseline and Change from Baseline in HAMD Total Score by Centre Group
Adjusting for the Effect of Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Intention to Treat Population

Centre Group = 002/004

	Treatment Groups						Pairwise Comparisons	
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo	Paroxetine IR vs Placebo
	Mean (s.e.) N		Mean (s.e.) N		Mean (s.e.) N		Mean (95% C.I.)	Mean (95% C.I.)
Baseline	24.6 (1.16)	8	24.1 (1.27)	8	25.8 (1.13)	8		
Week 1	-1.6 (0.92)	8	-0.0 (0.96)	8	-1.1 (1.18)	8		
Week 2	-9.5 (1.79)	8	-5.8 (1.93)	7	-1.7 (2.44)	7		
Week 3	-11.6 (1.75)	8	-10.6 (1.83)	8	-2.0 (2.36)	7		
Week 4	-13.6 (2.34)	8	-12.0 (2.44)	8	-2.8 (3.09)	7	-11 (-17.71, -3.85)	-9.2 (-15.80, -2.58)
Week 6	-13.6 (2.97)	7	-12.1 (2.74)	8	-0.8 (3.35)	8		
Week 8	-18.1 (2.31)	8	-13.9 (2.42)	8	2.4 (4.25)	5	-20 (-30.07,-10.79)	-16 (-25.05, -7.45)
Week 12	-19.6 (2.34)	8	-14.6 (2.70)	7	6.1 (3.38)	6	-26 (-33.92,-17.50)	-21 (-28.82,-12.52)
70% End Point	-14.9 (2.65)	8	-12.3 (2.77)	8	-1.1 (3.41)	8	-14 (-21.43, -6.10)	-11 (-18.52, -3.86)
Wk 12 End Point	-19.4 (2.49)	8	-15.4 (2.60)	8	2.5 (3.20)	8	-22 (-29.08,-14.68)	-18 (-24.79,-11.02)

Note: Only patients with a baseline and at least one post baseline assessment.

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1_NEW.SAS (25AUG97 15:12)

Table 1.4.1 (a)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
justing for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
seline	2.8	(0.06)	102	2.9	(0.06)	104	2.9	(0.06)	101						
ek 1	-0.1	(0.10)	100	-0.1	(0.10)	103	-0.0	(0.10)	100	-0.1	(-0.29, 0.06)	0.188	-0.1	(-0.25, 0.10)	0.411
ek 2	-0.8	(0.14)	88	-0.6	(0.14)	84	-0.6	(0.14)	96	-0.3	(-0.52, -0.03)	0.026	-0.0	(-0.29, 0.21)	0.740
ek 3	-1.2	(0.15)	87	-1.0	(0.15)	87	-0.8	(0.15)	91	-0.5	(-0.74, -0.21)	<0.001	-0.2	(-0.48, 0.06)	0.130
ek 4	-1.5	(0.16)	86	-1.2	(0.16)	83	-1.1	(0.16)	93	-0.4	(-0.68, -0.12)	0.005	-0.1	(-0.41, 0.16)	0.405
ek 6	-1.9	(0.17)	78	-1.7	(0.16)	78	-1.1	(0.16)	87	-0.7	(-1.01, -0.43)	<0.001	-0.6	(-0.86, -0.27)	<0.001
ek 8	-1.9	(0.17)	80	-1.8	(0.17)	70	-1.3	(0.17)	79	-0.6	(-0.90, -0.28)	<0.001	-0.5	(-0.85, -0.20)	0.002
ek 12	-2.0	(0.19)	66	-1.9	(0.19)	57	-1.3	(0.18)	67	-0.7	(-1.04, -0.35)	<0.001	-0.6	(-0.94, -0.20)	0.002
% End Point	-1.6	(0.16)	102	-1.4	(0.16)	104	-1.0	(0.16)	101	-0.6	(-0.88, -0.33)	<0.001	-0.4	(-0.66, -0.11)	0.007
12 End Point	-1.8	(0.19)	102	-1.5	(0.19)	104	-1.2	(0.19)	101	-0.6	(-0.91, -0.26)	<0.001	-0.3	(-0.65, -0.00)	0.049

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1_5_NEW.SAS (26AUG97 11:42)

Table 1.4.1 (6)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups									Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	94	2.9	(0.07)	96	2.9	(0.06)	93						
Week 1	-0.1	(0.11)	92	-0.1	(0.11)	95	-0.0	(0.11)	92	-0.1	(-0.27, 0.10)	0.382	-0.1	(-0.27, 0.11)	0.408
Week 2	-0.8	(0.15)	80	-0.6	(0.15)	77	-0.6	(0.14)	89	-0.2	(-0.49, 0.04)	0.090	-0.0	(-0.28, 0.26)	0.943
Week 3	-1.2	(0.16)	79	-0.9	(0.16)	79	-0.8	(0.15)	84	-0.4	(-0.69, -0.12)	0.005	-0.1	(-0.42, 0.16)	0.369
Week 4	-1.5	(0.17)	78	-1.2	(0.17)	75	-1.1	(0.16)	86	-0.4	(-0.67, -0.08)	0.014	-0.1	(-0.39, 0.22)	0.596
Week 6	-1.8	(0.17)	71	-1.6	(0.17)	70	-1.1	(0.17)	79	-0.7	(-0.98, -0.36)	<0.001	-0.5	(-0.84, -0.21)	0.001
Week 8	-1.8	(0.18)	72	-1.8	(0.18)	62	-1.3	(0.17)	74	-0.5	(-0.86, -0.19)	0.002	-0.4	(-0.79, -0.10)	0.012
Week 12	-1.9	(0.20)	58	-1.8	(0.19)	50	-1.4	(0.19)	61	-0.5	(-0.83, -0.10)	0.012	-0.4	(-0.79, -0.01)	0.043
LOCF End Point	-1.5	(0.17)	94	-1.3	(0.16)	96	-1.0	(0.16)	93	-0.6	(-0.84, -0.26)	<0.001	-0.3	(-0.63, -0.05)	0.021
Week 12 End Point	-1.7	(0.20)	94	-1.4	(0.19)	96	-1.2	(0.19)	93	-0.4	(-0.77, -0.09)	0.013	-0.2	(-0.52, 0.16)	0.296

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Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_1_5W_NEW.SAS (26AUG97 11:41)

Paroxetine CR - Protocol: 448

Table 1.4.2 (a)

Baseline and Change from Baseline in HAMD Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	102	2.9	(0.06)	104	2.9	(0.06)	101						
Week 2 LOCF	-0.8	(0.14)	102	-0.6	(0.13)	104	-0.6	(0.13)	101	-0.2	(-0.45, 0.01)	0.062	-0.1	(-0.31, 0.15)	0.488
Week 4 LOCF	-1.4	(0.16)	102	-1.1	(0.16)	104	-1.0	(0.16)	101	-0.3	(-0.62, -0.07)	0.014	-0.1	(-0.35, 0.20)	0.608
Week 6 LOCF	-1.6	(0.17)	102	-1.4	(0.17)	104	-1.0	(0.16)	101	-0.6	(-0.88, -0.32)	<0.001	-0.4	(-0.69, -0.13)	0.005
Week 8 LOCF	-1.7	(0.19)	102	-1.5	(0.18)	104	-1.2	(0.18)	101	-0.5	(-0.82, -0.20)	0.001	-0.3	(-0.60, 0.03)	0.071
Week 12 LOCF	-1.8	(0.19)	102	-1.5	(0.19)	104	-1.2	(0.19)	101	-0.6	(-0.91, -0.26)	<0.001	-0.3	(-0.65, -0.00)	0.049

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LOCF1415.SAS (04SEP97 14:39)

Paroxetine CR - Protocol: 448

Table 1.4.2 (b)

Baseline and Change from Baseline in HAMD Mood Item Score
Excluding Centre Group 002/004
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.8	(0.06)	94	2.9	(0.07)	96	2.9	(0.06)	93						
Week 2 LOCF	-0.7	(0.14)	94	-0.6	(0.14)	96	-0.6	(0.14)	93	-0.2	(-0.40, 0.09)	0.213	-0.0	(-0.29, 0.20)	0.697
Week 4 LOCF	-1.3	(0.17)	94	-1.0	(0.16)	96	-1.0	(0.16)	93	-0.3	(-0.58, -0.01)	0.046	-0.0	(-0.31, 0.27)	0.899
Week 6 LOCF	-1.5	(0.17)	94	-1.3	(0.17)	96	-1.0	(0.17)	93	-0.5	(-0.84, -0.25)	<0.001	-0.4	(-0.67, -0.07)	0.015
Week 8 LOCF	-1.6	(0.19)	94	-1.4	(0.19)	96	-1.2	(0.18)	93	-0.4	(-0.77, -0.12)	0.008	-0.2	(-0.53, 0.13)	0.240
Week 12 LOCF	-1.7	(0.20)	94	-1.4	(0.19)	96	-1.2	(0.19)	93	-0.4	(-0.77, -0.09)	0.013	-0.2	(-0.52, 0.16)	0.296

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LOCF1415W.SAS (04SEP97 15:05)

Paroxetine CR - Protocol : 448
Figure 1.4.3
Cumulative Frequency Distribution
HAMD Mood Item Score
Change from Baseline at Endpoint

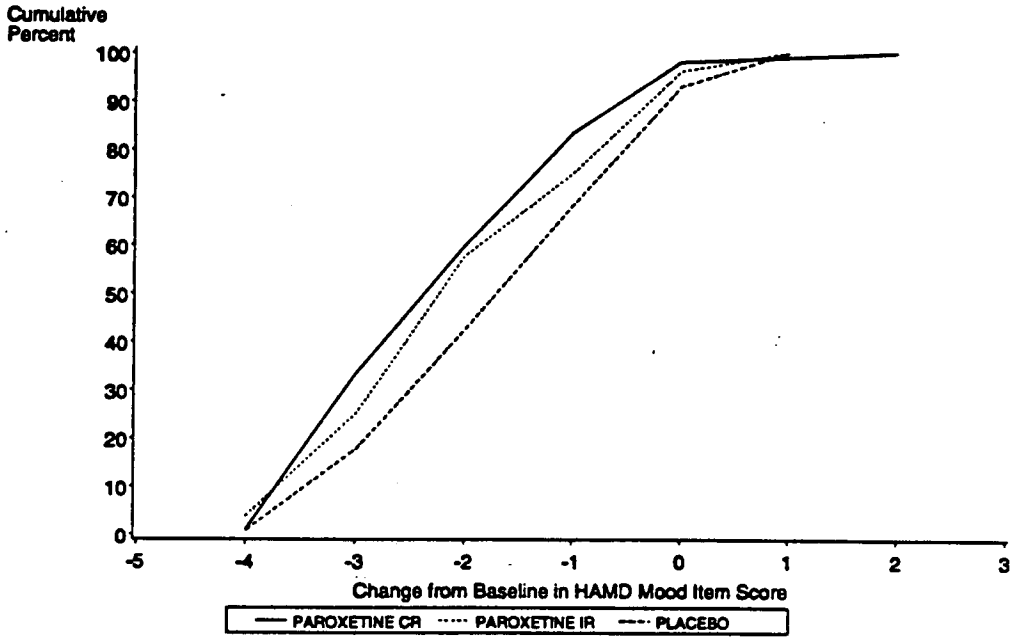

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Table 1.5.1 (a)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value		Median (95% C.I.)	p-value	
Baseline	4	96	4	100	4	99						
Week 1	0	91	0	99	0	96	0 (0.0, 0.0)	0.791		0 (0.0, 0.0)	0.940	
Week 2	0	80	0	81	0	92	0 (0.0, 0.0)	0.314		0 (0.0, 0.0)	0.723	
Week 3	-1	78	-1	85	-1	87	0 (0.0, 0.0)	0.279		0 (0.0, 0.0)	0.400	
Week 4	-1	77	-1	81	-1	89	0 (-1.0, 0.0)	0.148		0 (0.0, 0.0)	0.573	
Week 6	-1	71	-1	77	-1	84	-1 (-1.0, 0.0)	0.006		0 (-1.0, 0.0)	0.042	
Week 8	-2	73	-2	70	-1	75	-1 (-1.0, 0.0)	0.008		0 (-1.0, 0.0)	0.037	
Week 12	-2	64	-2	57	-1	65	-1 (-1.0, 0.0)	0.002		0 (-1.0, 0.0)	0.081	
LOCF End Point	-1	93	-1	100	-1	97	0 (-1.0, 0.0)	0.042		0 (0.0, 0.0)	0.436	
Wk 12 End Point	-2	96	-1	100	-1	99	-1 (-1.0, 0.0)	0.008		0 (-1.0, 0.0)	0.279	

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_2N.SAS (05SEP97 15:25)

Paroxetine CR - Protocol: 448

1

Table 1.5.1(b)

Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Centre Group 002/004
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median	(95% C.I.)	p-value	Median	(95% C.I.)	p-value
·aseline	4	88	4	94	4	91						
·eek 1	0	83	0	91	0	88	0	(0.0, 0.0)	0.782	0	(0.0, 0.0)	0.947
·eek 2	0	72	0	74	0	85	0	(0.0, 0.0)	0.638	0	(0.0, 0.0)	0.870
·eek 3	-1	70	-1	77	-1	80	0	(0.0, 0.0)	0.726	0	(0.0, 0.0)	0.995
·eek 4	-1	69	-1	73	-1	82	0	(-1.0, 0.0)	0.320	0	(0.0, 0.0)	0.816
·eek 6	-1	64	-1	69	-1	76	0	(-1.0, 0.0)	0.033	0	(-1.0, 0.0)	0.111
·eek 8	-2	65	-1.5	62	-1	70	0	(-1.0, 0.0)	0.033	0	(-1.0, 0.0)	0.143
·eek 12	-2	56	-2	50	-2	59	0	(-1.0, 0.0)	0.045	0	(-1.0, 0.0)	0.357
·0% End Point	-1	85	-1	92	-1	89	0	(-1.0, 0.0)	0.137	0	(0.0, 0.0)	0.665
·k 12 End Point	-2	88	-1	92	-1	91	0	(-1.0, 0.0)	0.085	0	(0.0, 0.0)	0.785

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Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LT14_2W.SAS (22AUG97 15:53)

Table 1.5.2(a)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(Min,Max)	N	Median (95% C.I.)	p-value		Median (95% C.I.)	p-value	
eline	4		96	4		100	4		99						
k 2 LOCF	0		93	0		100	0		97	0 (0.0, 0.0)	0.570		0 (0.0, 0.0)	0.979	
k 4 LOCF	-1		93	-1		100	-1		97	0 (0.0, 0.0)	0.448		0 (0.0, 0.0)	0.900	
k 6 LOCF	-1		93	-1		100	-1		97	0 (-1.0, 0.0)	0.046		0 (0.0, 0.0)	0.307	
k 8 LOCF	-1.5		94	-1		100	-1		97	0 (-1.0, 0.0)	0.035		0 (-1.0, 0.0)	0.371	
k 12 LOCF	-2		96	-1		100	-1		99	-1 (-1.0, 0.0)	0.008		0 (-1.0, 0.0)	0.279	

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Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.448.CODE]LOCF14_2.SAS (05SEP97 10:23)

Paroxetine CR - Protocol: 448

Table 1.5.2(b)

Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Centre Group 002/004
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(Min,Max)	N	Median (95% C.I.)	p-value		Median (95% C.I.)	p-value	
eline	4		88	4		92	4		91						
k 2 LOCF	0		85	0		92	0		89	0 (0.0, 0.0)	0.980		0 (0.0, 0.0)	0.586	
k 4 LOCF	-1		85	-1		92	-1		89	0 (0.0, 0.0)	0.792		0 (0.0, 0.0)	0.618	
k 6 LOCF	-1		85	-1		92	-1		89	0 (-1.0, 0.0)	0.163		0 (0.0, 0.0)	0.522	
k 8 LOCF	-1		86	-1		92	-1		89	0 (-1.0, 0.0)	0.120		0 (0.0, 0.0)	0.764	
k 12 LOCF	-2		88	-1		92	-1		91	0 (-1.0, 0.0)	0.085		0 (0.0, 0.0)	0.785	

Note: Only patients with a baseline and at least one post baseline assessment

Paroxetine CR - Protocol : 448
Figure 1.5.3
Cumulative Frequency Distribution
CGI Severity Score
Change from Baseline at Endpoint

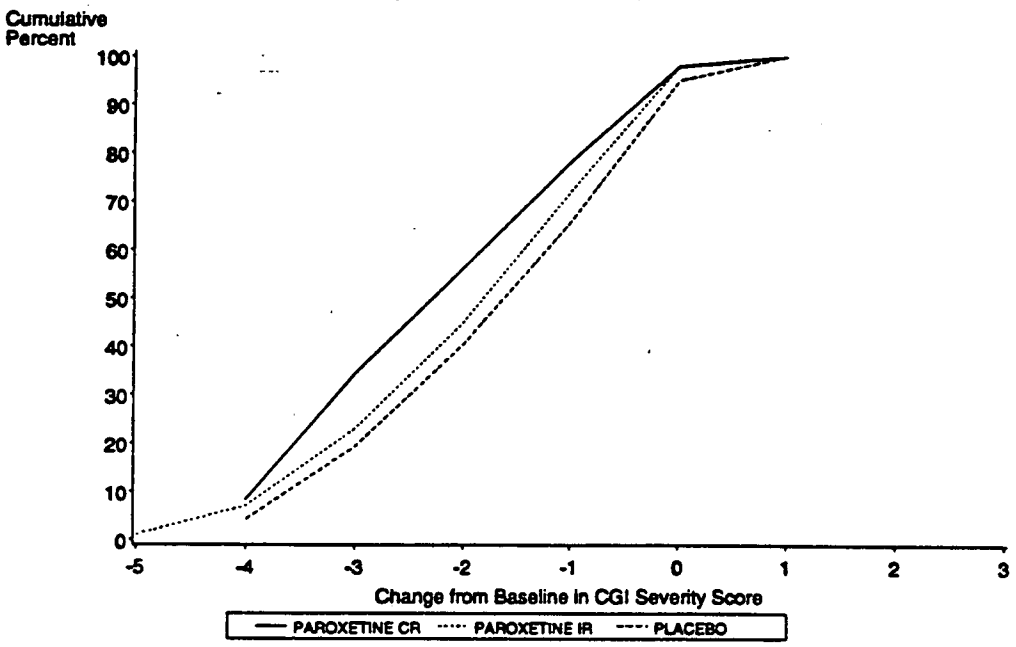


Table 2.1.1.

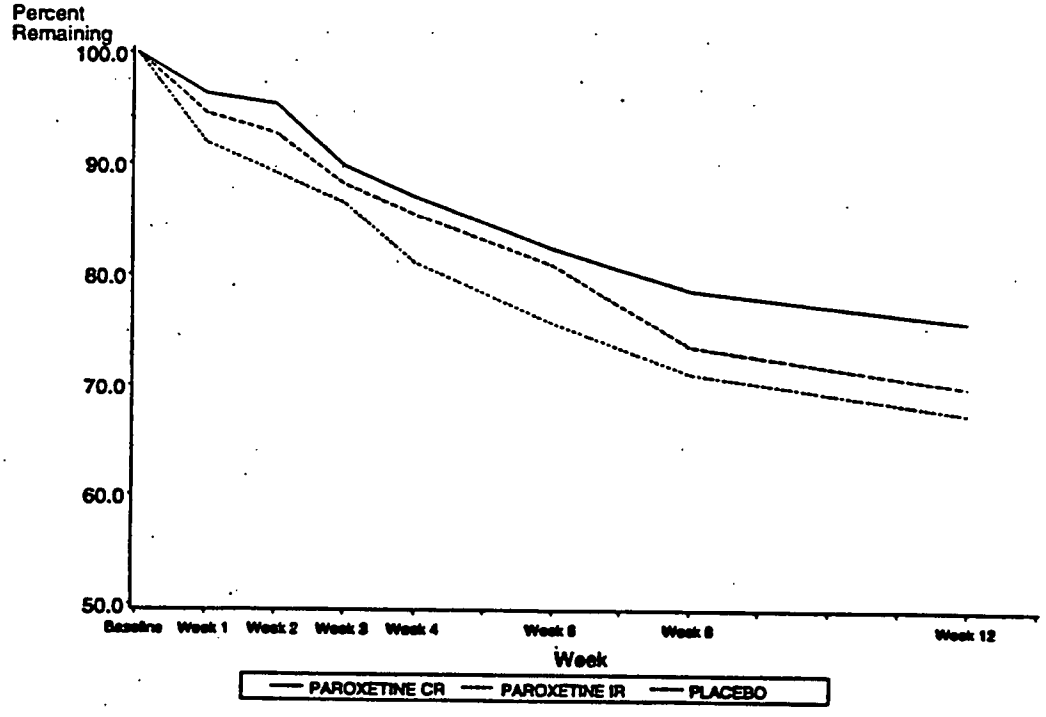
Table . Number of Patients Remaining at Each Visit for PAR-449

Study Phase	Paroxetine CR		Paroxetine IR		Placebo		Total	
	n	%	n	%	n	%	n	%
Baseline	108	100.0	112	100.0	110	100.0	330	100.0
Week 1	104	96.3	102	91.1	104	94.5	310	93.9
Week 2	103	95.4	99	88.4	102	92.7	304	92.1
Week 3	97	89.8	96	85.7	97	88.2	290	87.9
Week 4	94	87.0	90	80.4	94	85.5	278	84.2
Week 6	89	82.4	84	75.0	89	80.9	262	79.4
Week 8	85	78.7	79	70.5	81	73.6	245	74.2
Week 12	81	75.0	75	67.0	77	70.0	234	70.6

Data Source: PAR-449. Data Source Table 13.3.2b

Figure 2.1.1

Figure Percentage of Patients Remaining in Study 449 by Week



Data Source: PAR-449 Data Source Figure 13.3.2

Paroxetine CR - Protocol: 449

2.3.1(a)

Table

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

	Treatment Groups								Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo	
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	23.8	(0.33)	108	23.7	(0.29)	110	23.5	(0.30)	110						
Week 1	-6.0	(0.47)	106	-5.5	(0.46)	108	-6.1	(0.45)	109	0.2	(-1.07, 1.39)	0.798	0.7	(-0.57, 1.89)	0.292
Week 2	-7.0	(0.57)	101	-6.5	(0.57)	99	-5.9	(0.57)	102	-1.2	(-2.70, 0.36)	0.134	-0.6	(-2.19, 0.90)	0.412
Week 3	-9.0	(0.63)	98	-8.6	(0.64)	93	-8.3	(0.63)	98	-0.7	(-2.32, 1.02)	0.442	-0.3	(-2.02, 1.42)	0.730
Week 4	-10.8	(0.67)	95	-10.8	(0.68)	89	-9.9	(0.67)	93	-1.0	(-2.76, 0.81)	0.282	-0.9	(-2.76, 0.92)	0.326
Week 6	-12.9	(0.72)	93	-11.6	(0.73)	87	-10.0	(0.72)	91	-2.9	(-4.81, -0.99)	0.003	-1.6	(-3.57, 0.36)	0.109
Week 8	-14.7	(0.74)	83	-13.6	(0.74)	83	-11.0	(0.73)	87	-3.7	(-5.64, -1.73)	<0.001	-2.6	(-4.63, -0.64)	0.010
Week 12	-15.7	(0.86)	77	-13.9	(0.93)	66	-12.4	(0.89)	72	-3.3	(-5.59, -1.01)	0.005	-1.5	(-3.91, 0.99)	0.241
70% End Point	-12.7	(0.74)	108	-11.5	(0.72)	110	-9.6	(0.72)	110	-3.1	(-5.04, -1.15)	0.002	-1.9	(-3.87, 0.04)	0.055
Wk 12 End Point	-13.3	(0.79)	108	-12.1	(0.78)	110	-10.2	(0.78)	110	-3.1	(-5.18, -0.99)	0.004	-1.9	(-3.96, 0.24)	0.083

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LT14_1.SAS (07AUG97 19:41)

Table Table 2.3.1 (b)

Baseline and Change from Baseline in HAMD Total Score
Excluding Centre 017
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	23.9	(0.33)	103	23.9	(0.30)	104	23.7	(0.31)	104						
Week 1	-4.0	(0.49)	101	-3.6	(0.48)	102	-4.3	(0.48)	104	0.3	(-1.03, 1.53)	0.695	0.7	(-0.60, 1.98)	0.293
Week 2	-6.9	(0.59)	97	-6.7	(0.60)	93	-6.0	(0.59)	97	-0.9	(-2.51, 0.65)	0.246	-0.7	(-2.34, 0.87)	0.369
Week 3	-9.0	(0.65)	94	-8.9	(0.67)	87	-8.4	(0.64)	95	-0.6	(-2.31, 1.11)	0.493	-0.4	(-2.21, 1.35)	0.635
Week 4	-11.0	(0.69)	90	-11.1	(0.71)	83	-10.1	(0.69)	89	-0.9	(-2.76, 0.90)	0.317	-1.0	(-2.88, 0.93)	0.314
Week 6	-13.1	(0.74)	88	-12.0	(0.76)	82	-10.2	(0.74)	87	-2.8	(-4.78, -0.85)	0.005	-1.7	(-3.76, 0.31)	0.097
Week 8	-14.8	(0.77)	78	-14.1	(0.78)	78	-11.1	(0.74)	84	-3.7	(-5.74, -1.73)	<0.001	-3.0	(-5.05, -0.92)	0.005
Week 12	-15.8	(0.87)	74	-14.3	(0.96)	63	-12.4	(0.90)	71	-3.3	(-5.65, -1.02)	0.005	-1.9	(-4.35, 0.62)	0.140
LOCF End Point	-12.8	(0.76)	103	-11.8	(0.76)	104	-9.8	(0.75)	104	-3.0	(-5.05, -1.00)	0.004	-2.0	(-4.05, 0.03)	0.054
Wk 12 End Point	-13.3	(0.82)	103	-12.3	(0.81)	104	-10.4	(0.81)	104	-3.0	(-5.13, -0.79)	0.008	-2.0	(-4.15, 0.23)	0.080

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LT14_1_FIDDES.SAS (26AUG97 17:44)

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Table 2.3.2 (a)

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)	p-value		Mean (95% C.I.)	p-value	
Baseline	23.8	(0.33)	108	23.7	(0.29)	110	23.5	(0.30)	110						
Week 2 LOCF	-6.8	(0.55)	108	-6.2	(0.54)	110	-5.7	(0.54)	110	-1.1 (-2.53, 0.39)	0.149		-0.5 (-1.93, 1.01)	0.539	
Week 4 LOCF	-9.9	(0.65)	108	-9.9	(0.63)	110	-8.9	(0.64)	110	-1.0 (-2.71, 0.71)	0.250		-1.0 (-2.70, 0.74)	0.262	
Week 6 LOCF	-11.3	(0.70)	108	-10.4	(0.69)	110	-8.8	(0.69)	110	-2.4 (-4.31, -0.59)	0.010		-1.6 (-3.49, 0.25)	0.089	
Week 8 LOCF	-12.7	(0.73)	108	-11.8	(0.72)	110	-9.6	(0.72)	110	-3.1 (-5.08, -1.21)	0.002		-2.3 (-4.22, -0.33)	0.022	
Week 12 LOCF	-13.3	(0.79)	108	-12.1	(0.78)	110	-10.2	(0.78)	110	-3.1 (-5.18, -0.99)	0.004		-1.9 (-3.96, 0.24)	0.083	

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LOCF14_1.SAS (04SEP97 13:12)

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9.2 Cumulative Frequency Distribution Plots

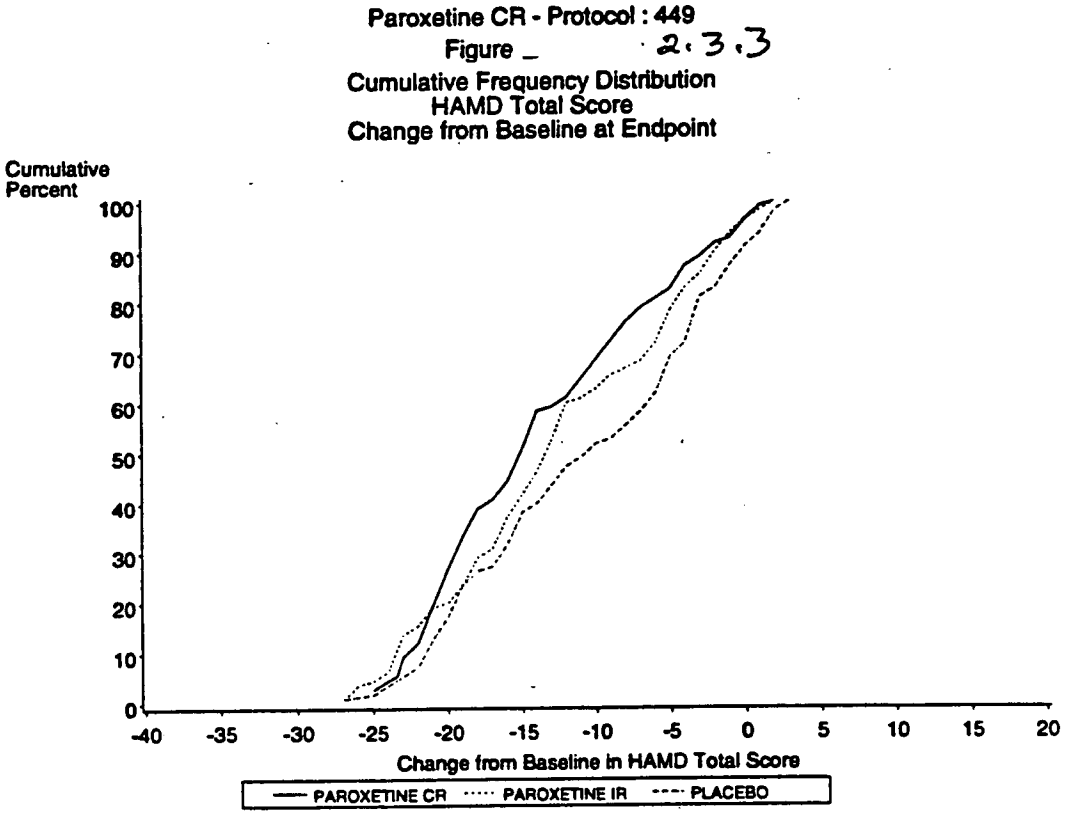

Figure 14.1.18.1 presents the cumulative frequency distribution of the change from baseline in HAMD total score. Paroxetine CR patients had the highest gradient, with placebo the least steep of the three. All three cumulative distributions were reasonably linear. Figure 14.4.18.1 is similar to above, but this plots change from baseline in mood item score only. Much the same trend is shown in this figure, although there is arguably more suggestion of a difference in response between the two active treatments and placebo. Finally, Figure 14.6.1.1 shows the cumulative frequency distribution of the change from baseline in CGI Severity score. Again there is some suggestion of a difference between paroxetine CR and placebo, but less so between paroxetine IR and placebo.

Table 2.4.1(a)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
djusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
aseline	2.9	(0.06)	108	2.9	(0.06)	110	2.8	(0.06)	110						
eek 1	-0.3	(0.12)	106	-0.2	(0.12)	108	-0.1	(0.12)	109	-0.2	(-0.41, 0.03)	0.098	-0.1	(-0.37, 0.07)	0.191
eek 2	-0.4	(0.16)	101	-0.4	(0.17)	99	-0.1	(0.16)	102	-0.3	(-0.60, -0.05)	0.021	-0.3	(-0.54, 0.01)	0.057
eek 3	-0.8	(0.17)	98	-0.9	(0.17)	93	-0.7	(0.17)	98	-0.2	(-0.45, 0.12)	0.250	-0.2	(-0.49, 0.09)	0.182
eek 4	-1.1	(0.18)	95	-1.1	(0.18)	89	-0.8	(0.19)	93	-0.3	(-0.54, 0.03)	0.082	-0.3	(-0.56, 0.02)	0.069
eek 6	-1.3	(0.21)	93	-1.3	(0.21)	87	-0.7	(0.21)	91	-0.5	(-0.81, -0.24)	<0.001	-0.6	(-0.84, -0.26)	<0.001
eek 8	-1.7	(0.26)	83	-1.6	(0.27)	83	-1.1	(0.27)	87	-0.6	(-0.92, -0.34)	<0.001	-0.5	(-0.80, -0.20)	<0.001
eek 12	-1.4	(0.29)	77	-1.3	(0.31)	66	-1.0	(0.31)	72	-0.4	(-0.77, -0.08)	0.016	-0.3	(-0.62, 0.11)	0.169
0% End Point	-1.4	(0.16)	108	-1.2	(0.17)	110	-0.8	(0.16)	110	-0.6	(-0.88, -0.29)	<0.001	-0.4	(-0.70, -0.11)	0.008
k 12 End Point	-1.3	(0.17)	108	-1.2	(0.18)	110	-0.8	(0.17)	110	-0.5	(-0.81, -0.18)	0.002	-0.4	(-0.70, -0.07)	0.017

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LT14_1_5.SAS (14AUG97 20:44)

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Table 2.4.1 (b)

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Excluding Centre 017
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.9	(0.06)	103	2.9	(0.06)	106	2.8	(0.06)	104						
Week 1	-0.3	(0.13)	101	-0.3	(0.13)	102	-0.2	(0.13)	104	-0.2	(-0.40, 0.07)	0.167	-0.2	(-0.41, 0.07)	0.157
Week 2	-0.4	(0.16)	97	-0.4	(0.17)	93	-0.1	(0.16)	97	-0.3	(-0.57, -0.02)	0.035	-0.3	(-0.61, -0.04)	0.023
Week 3	-0.9	(0.17)	94	-1.0	(0.17)	87	-0.7	(0.17)	95	-0.2	(-0.46, 0.12)	0.257	-0.2	(-0.54, 0.06)	0.113
Week 4	-1.2	(0.18)	90	-1.2	(0.18)	83	-0.9	(0.19)	89	-0.2	(-0.52, 0.05)	0.110	-0.3	(-0.59, 0.00)	0.051
Week 6	-1.3	(0.21)	88	-1.4	(0.21)	82	-0.8	(0.21)	87	-0.5	(-0.80, -0.22)	<0.001	-0.6	(-0.89, -0.29)	<0.001
Week 8	-1.7	(0.26)	78	-1.7	(0.26)	78	-1.1	(0.26)	84	-0.6	(-0.92, -0.34)	<0.001	-0.6	(-0.88, -0.28)	<0.001
Week 12	-1.5	(0.29)	74	-1.4	(0.31)	63	-1.0	(0.30)	71	-0.4	(-0.77, -0.08)	0.017	-0.4	(-0.72, 0.02)	0.061
70% End Point	-1.4	(0.16)	103	-1.3	(0.17)	106	-0.8	(0.16)	106	-0.5	(-0.85, -0.24)	<0.001	-0.4	(-0.75, -0.14)	0.004
Wk 12 End Point	-1.2	(0.17)	103	-1.2	(0.18)	106	-0.8	(0.17)	104	-0.5	(-0.77, -0.13)	0.006	-0.4	(-0.76, -0.11)	0.009

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LT14_1_5_FIDDES.SAS (26AUG97 18:56)

Table 2.4.2

Baseline and Change from Baseline in HAMD Mood Item Score
ljusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean (95% C.I.)	p-value		Mean (95% C.I.)	p-value	
seline	2.9	(0.06)	108	2.9	(0.06)	110	2.8	(0.06)	110						
ek 2 LOCF	-0.5	(0.14)	108	-0.4	(0.15)	110	-0.2	(0.14)	110	-0.3 (-0.56, -0.04)	0.025		-0.2 (-0.47, 0.06)	0.126	
ek 4 LOCF	-1.1	(0.15)	108	-1.1	(0.16)	110	-0.8	(0.15)	110	-0.3 (-0.53, 0.03)	0.077		-0.3 (-0.56, -0.00)	0.050	
ek 6 LOCF	-1.2	(0.16)	108	-1.2	(0.16)	110	-0.7	(0.15)	110	-0.4 (-0.73, -0.16)	0.002		-0.5 (-0.81, -0.24)	<0.001	
ek 8 LOCF	-1.4	(0.16)	108	-1.2	(0.16)	110	-0.8	(0.16)	110	-0.6 (-0.87, -0.29)	<0.001		-0.5 (-0.75, -0.17)	0.002	
ek 12 LOCF	-1.3	(0.17)	108	-1.2	(0.18)	110	-0.8	(0.17)	110	-0.5 (-0.81, -0.18)	0.002		-0.4 (-0.70, -0.07)	0.017	

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LOCF1415.SAS (04SEP97 13:16)

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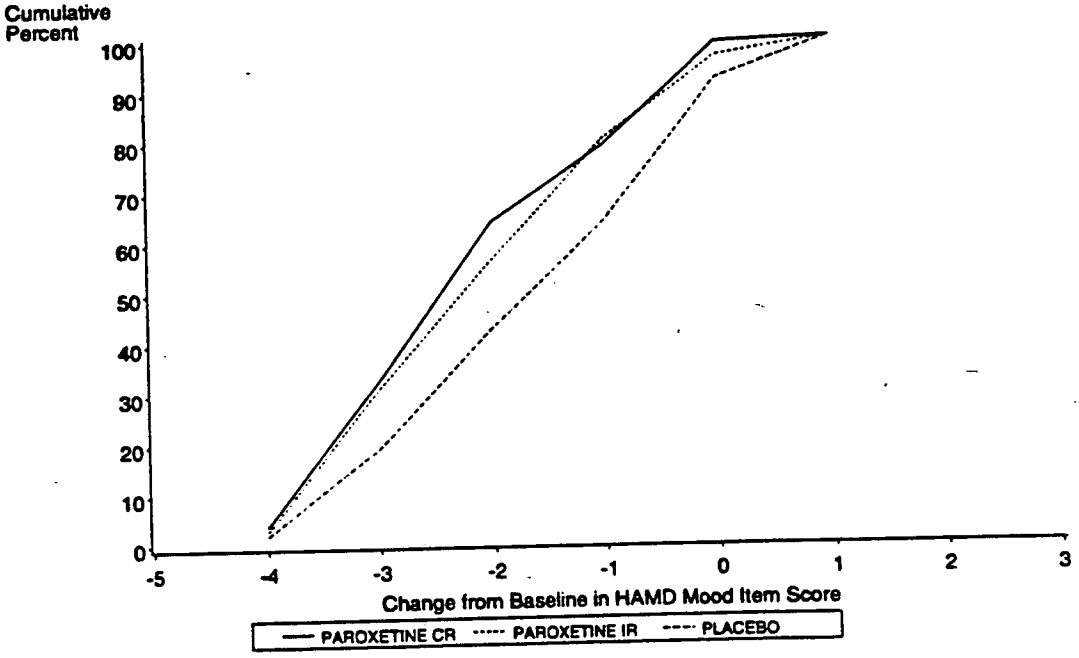
Paroxetine CR - Protocol : 449
Figure 2.4.3
Cumulative Frequency Distribution
HAMD Mood Item Score
Change from Baseline at Endpoint



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Tabl 2.5.1(a)

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max)	N	Median	(Min,Max)	N	Median	(Min,Max)	N	Median (95% C.I.)	p-value		Median (95% C.I.)	p-value	
Baseline	4		99	4		102	4		99						
Week 1	0		97	0		99	0		96	0 (0.0, 0.0)	0.104		0 (0.0, 0.0)	0.424	
Week 2	0		92	0		90	0		93	0 (0.0, 0.0)	0.942		0 (0.0, 0.0)	0.857	
Week 3	-0.5		90	-1		85	-1		90	0 (0.0, 0.0)	0.574		0 (0.0, 0.0)	0.578	
Week 4	-1		87	-1		83	-1		83	0 (-1.0, 0.0)	0.227		0 (-1.0, 0.0)	0.102	
Week 6	-1		84	-1		79	-1		83	0 (-1.0, 0.0)	0.040		0 (-1.0, 0.0)	0.327	
Week 8	-2		76	-2		76	-1		79	-1 (-1.0, 0.0)	0.007		0 (-1.0, 0.0)	0.066	
Week 12	-2		70	-2		60	-2		64	0 (-1.0, 0.0)	0.147		0 (-1.0, 0.0)	0.638	
70% End Point	-1		99	-1		102	-1		98	0 (-1.0, 0.0)	0.013		0 (-1.0, 0.0)	0.135	
Wk 12 End Point	-2		99	-2		102	-1		98	0 (-1.0, 0.0)	0.042		0 (-1.0, 0.0)	0.335	

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LT14_2.SAS (14AUG97 20:59)

Table 2.5.1(b)

Baseline and Change from Baseline in CGI Severity of Illness Score
Excluding Centre 017
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons			
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo		Paroxetine IR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.) p-value		Median (95% C.I.) p-value	
Baseline	4	94	4	96	4	93				
Week 1	0	92	0	93	0	92	0 (0.0, 0.0)	0.111	0 (0.0, 0.0)	0.472
Week 2	0	88	0	84	0	88	0 (0.0, 0.0)	0.883	0 (0.0, 0.0)	0.810
Week 3	-1	86	-1	79	-1	87	0 (0.0, 0.0)	0.627	0 (0.0, 0.0)	0.473
Week 4	-1	82	-1	77	-1	79	0 (-1.0, 0.0)	0.285	0 (-1.0, 0.0)	0.139
Week 6	-1	79	-1	74	-1	79	0 (-1.0, 0.0)	0.042	0 (-1.0, 0.0)	0.359
Week 8	-2	71	-2	71	-1	76	-1 (-1.0, 0.0)	0.009	0 (-1.0, 0.0)	0.063
Week 12	-2	67	-2	57	-2	63	0 (-1.0, 0.0)	0.148	0 (-1.0, 0.0)	0.515
70% End Point	-1.5	94	-1	96	-1	93	0 (-1.0, 0.0)	0.022	0 (-1.0, 0.0)	0.189
Wk 12 End Point	-2	94	-2	96	-1	93	0 (-1.0, 0.0)	0.074	0 (-1.0, 0.0)	0.395

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LT14_2_FIDDESN.SAS (05SEP97 15:44)

Paroxetine CR - Protocol: 449

Table 2.5.2

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons			
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo		Paroxetine IR vs Placebo	
	Median (Min,Max)	N	Median (Min,Max)	N	Median (Min,Max)	N	Median (95% C.I.)	p-value	Median (95% C.I.)	p-value
Baseline	4	99	4	102	4	98				
Week 2 LOCF	0	99	0	102	0	98	0 (0.0, 0.0)	0.775	0 (0.0, 0.0)	0.872
Week 4 LOCF	-1	99	-1	102	-1	98	0 (0.0, 0.0)	0.341	0 (-1.0, 0.0)	0.143
Week 6 LOCF	-1	99	-1	102	-1	98	0 (-1.0, 0.0)	0.065	0 (0.0, 0.0)	0.265
Week 8 LOCF	-1	99	-1	102	-1	98	0 (-1.0, 0.0)	0.013	0 (-1.0, 0.0)	0.076
Week 12 LOCF	-2	99	-2	102	-1	98	0 (-1.0, 0.0)	0.042	0 (-1.0, 0.0)	0.335

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.449.CODE]LOCF14_2.SAS (04SEP97 13:19)

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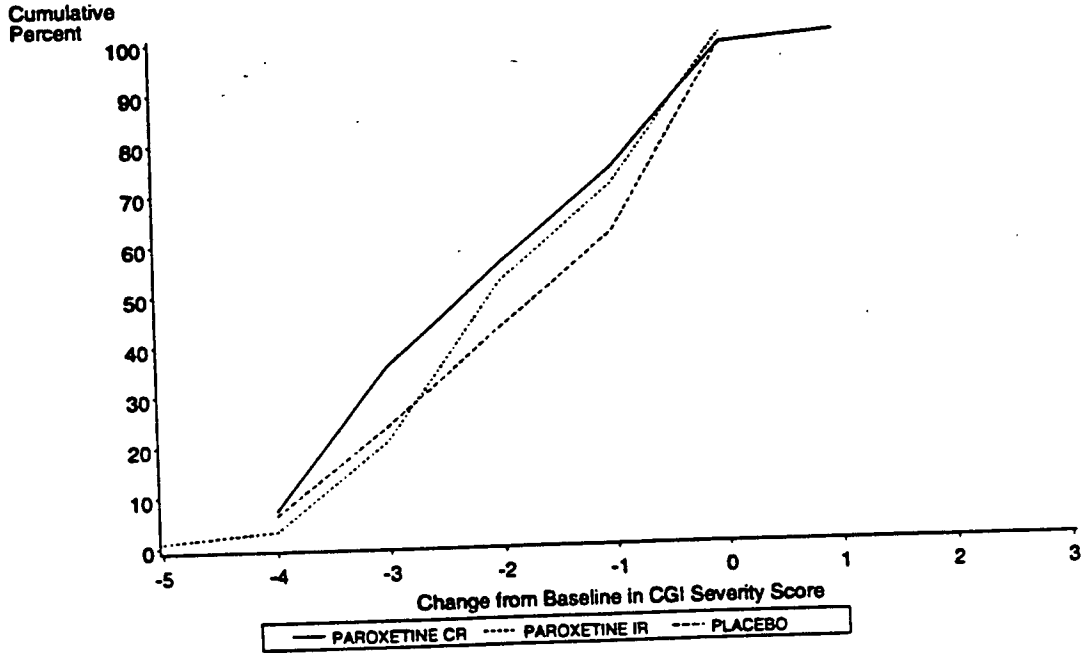
Paroxetine CR - Protocol : 449
Figure 2.5.3
Cumulative Frequency Distribution
CGI Severity Score
Change from Baseline at Endpoint



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3.1.1.

Table Number (%) of Patients in the ITT Population Entering Each Visit Window

	Paroxetine CR		Paroxetine IR		Placebo		Total	
	N	%	N	%	N	%	N	%
Baseline	104	100.0	106	100.0	109	100.0	319	100.0
Week 1	102	98.1	99	93.4	102	93.6	303	95.0
Week 2	97	93.3	97	91.5	99	90.8	293	91.8
Week 3	94	90.4	94	88.7	98	89.9	286	89.7
Week 4	90	86.5	90	84.9	97	89.0	277	86.8
Week 6	89	85.6	84	79.2	91	83.5	264	82.8
Week 8	84	80.8	79	74.5	90	82.6	253	79.3
Week 10	83	79.8	78	73.6	85	78.0	246	77.1
Week 12	81	77.9	77	72.6	84	77.1	242	75.9
Completed	81	77.9	76	71.7	84	77.1	241	75.5

Data Source: Data source Table 13.3.2b, 13.1.1, Appendix B, Listing 13.3b

8.1 Percentage of Patients Remaining in the Study by Week

Paroxetine CR - Protocol : 487

Figure 13.3.2

Percentage of Patients Remaining in the Study by Week

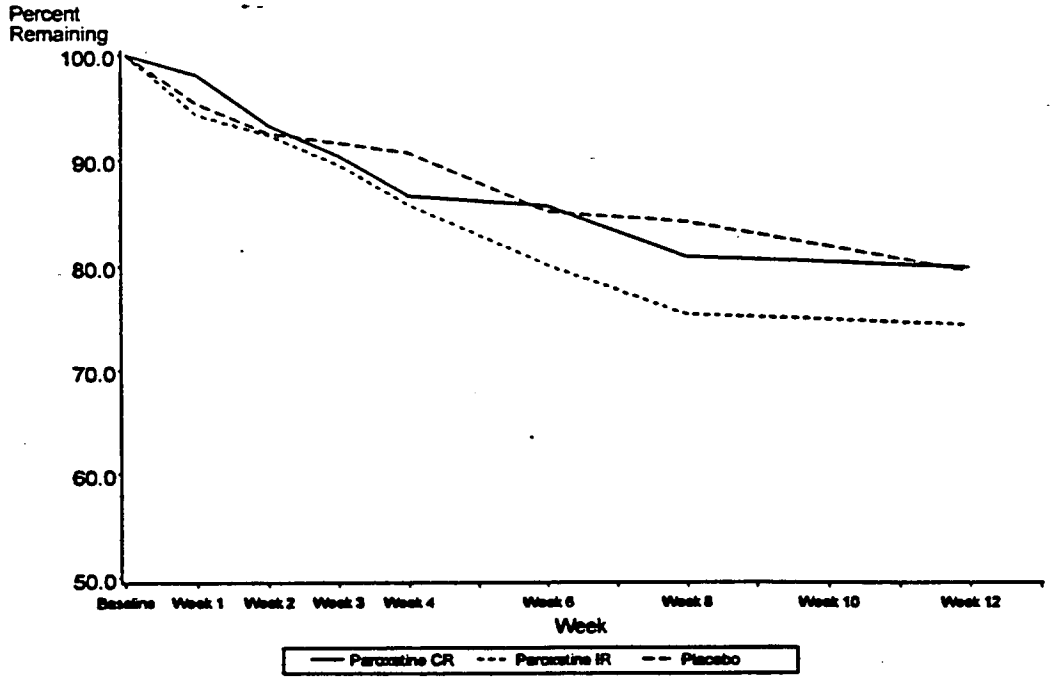

Table 3.3.1

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Total Score and Duration of Current Episode of Depression
Statistical Analysis Presented at all Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	22.1	(0.34)	103	22.3	(0.31)	103	22.1	(0.29)	107						
Week 1	-3.0	(0.44)	102	-3.7	(0.42)	102	-3.7	(0.43)	106	0.6	(-0.50, 1.76)	0.273	-0.0	(-1.15, 1.06)	0.936
Week 2	-5.8	(0.53)	98	-5.7	(0.53)	94	-5.5	(0.52)	98	-0.3	(-1.72, 1.05)	0.635	-0.2	(-1.62, 1.13)	0.730
Week 3	-9.4	(0.60)	90	-7.5	(0.58)	95	-7.4	(0.59)	91	-2.0	(-3.52, -0.41)	0.014	-0.1	(-1.57, 1.43)	0.930
Week 4	-9.9	(0.63)	93	-8.8	(0.62)	92	-8.7	(0.61)	97	-1.2	(-2.87, 0.40)	0.138	-0.2	(-1.75, 1.45)	0.851
Week 6	-11.5	(0.66)	86	-10.9	(0.64)	89	-9.1	(0.63)	94	-2.4	(-4.14, -0.71)	0.006	-1.8	(-3.45, -0.16)	0.031
Week 8	-12.9	(0.62)	85	-12.1	(0.62)	82	-10.7	(0.60)	89	-2.2	(-3.82, -0.59)	0.008	-1.5	(-3.06, 0.13)	0.072
Week 10	-13.8	(0.69)	83	-13.5	(0.68)	77	-10.6	(0.65)	90	-3.2	(-4.94, -1.41)	<0.001	-2.9	(-4.67, -1.16)	0.001
Week 12	-14.4	(0.70)	80	-13.9	(0.70)	73	-10.5	(0.68)	80	-3.8	(-5.65, -1.97)	<0.001	-3.4	(-5.18, -1.56)	<0.001
Wk 12 End Point	-12.1	(0.73)	103	-12.3	(0.70)	103	-9.5	(0.71)	107	-2.6	(-4.47, -0.73)	0.007	-2.8	(-4.65, -0.99)	0.003

Note: Only patients with a baseline and at least one post baseline assessment

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Table 3.3.2

Baseline and Change from Baseline in HAMD Total Score
Adjusting for the Effect of Centre Group Only
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

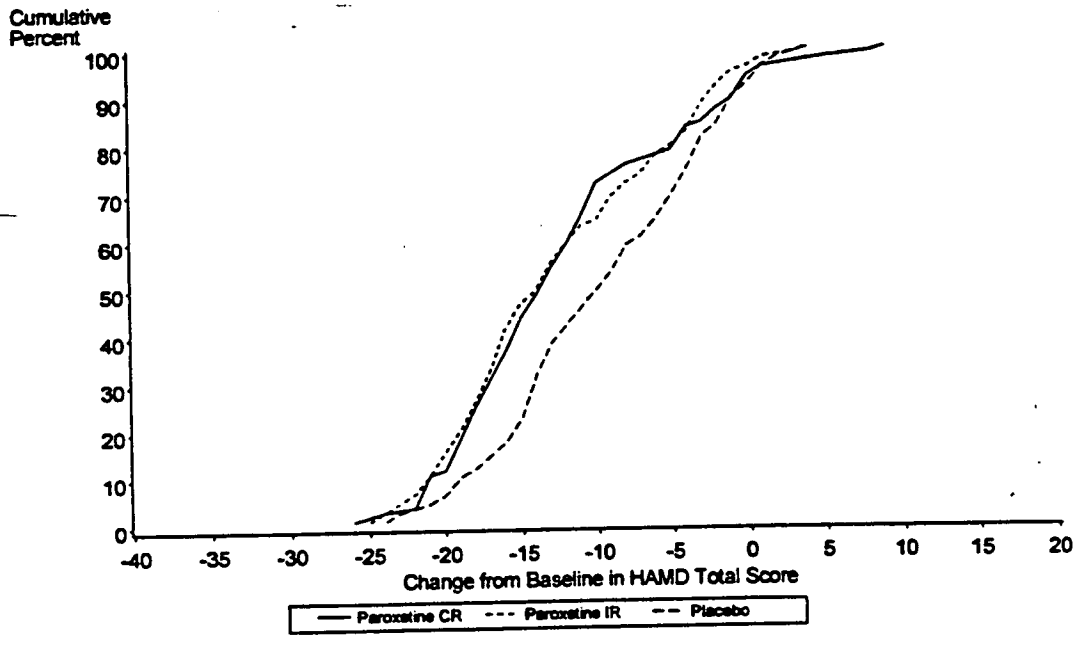
	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	22.1	(0.34)	103	22.3	(0.31)	103	22.1	(0.29)	107						
Week 2 LOCF	-5.9	(0.48)	103	-5.8	(0.48)	103	-5.4	(0.47)	107	-0.5	(-1.83, 0.80)	0.440	-0.4	(-1.68, 0.94)	0.581
Week 4 LOCF	-9.0	(0.60)	103	-8.4	(0.60)	103	-8.0	(0.59)	107	-1.0	(-2.62, 0.63)	0.230	-0.4	(-2.02, 1.24)	0.638
Week 6 LOCF	-10.1	(0.63)	103	-10.2	(0.62)	103	-8.5	(0.61)	107	-1.6	(-3.30, 0.09)	0.064	-1.7	(-3.36, 0.03)	0.054
Week 8 LOCF	-10.9	(0.64)	103	-10.7	(0.64)	103	-9.3	(0.63)	107	-1.6	(-3.30, 0.17)	0.078	-1.4	(-3.18, 0.30)	0.105
Week 10 LOCF	-11.4	(0.68)	103	-11.8	(0.67)	103	-9.3	(0.66)	107	-2.1	(-3.93, -0.25)	0.026	-2.5	(-4.38, -0.70)	0.007
Week 12 LOCF	-11.7	(0.69)	103	-12.1	(0.69)	103	-9.2	(0.67)	107	-2.5	(-4.37, -0.62)	0.009	-2.9	(-4.82, -1.07)	0.002

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.487.CODE]LOCF14_1.SAS (18NOV97 11:29)

8.2 Cumulative Frequency Distribution Plots

Paroxetine CR - Protocol : 487
Figure 3.3.3
Cumulative Frequency Distribution
HAMD Total Score
Change from Baseline at Endpoint



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Paroxetine CR - Protocol: 487

Table 3.4.1

Baseline and Change from Baseline in HAMD Depressed Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Depressed Mood Item and Duration of Current Episode of Depression
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.7	(0.06)	103	2.8	(0.06)	103	2.7	(0.06)	107						
Week 1	-0.2	(0.10)	102	-0.3	(0.10)	102	-0.1	(0.10)	106	-0.0	(-0.21, 0.19)	0.928	-0.1	(-0.32, 0.07)	0.202
Week 2	-0.6	(0.12)	98	-0.5	(0.13)	94	-0.5	(0.13)	98	-0.1	(-0.40, 0.10)	0.235	-0.0	(-0.29, 0.21)	0.742
Week 3	-0.9	(0.13)	90	-0.6	(0.13)	95	-0.7	(0.14)	91	-0.2	(-0.45, 0.10)	0.208	0.1	(-0.15, 0.38)	0.392
Week 4	-1.1	(0.14)	93	-1.0	(0.15)	92	-0.8	(0.14)	97	-0.4	(-0.65, -0.07)	0.014	-0.2	(-0.46, 0.11)	0.222
Week 6	-1.3	(0.13)	86	-1.1	(0.13)	89	-0.7	(0.13)	94	-0.5	(-0.81, -0.26)	<0.001	-0.4	(-0.64, -0.11)	0.005
Week 8	-1.4	(0.14)	85	-1.2	(0.14)	82	-0.9	(0.14)	89	-0.5	(-0.80, -0.24)	<0.001	-0.3	(-0.60, -0.04)	0.025
Week 10	-1.6	(0.14)	83	-1.7	(0.15)	77	-1.0	(0.14)	90	-0.6	(-0.93, -0.34)	<0.001	-0.7	(-0.96, -0.37)	<0.001
Week 12	-1.7	(0.15)	80	-1.6	(0.15)	73	-0.9	(0.15)	80	-0.7	(-1.06, -0.43)	<0.001	-0.6	(-0.93, -0.30)	<0.001
Wk 12 End Point	-1.4	(0.15)	103	-1.4	(0.15)	103	-0.9	(0.15)	107	-0.5	(-0.81, -0.22)	<0.001	-0.5	(-0.83, -0.26)	<0.001

Note: Only patients with a baseline and at least one post baseline assessment

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Paroxetine CR - Protocol: 487

Table 3.4.2

Baseline and Change from Baseline in HAMD Mood Item Score
Adjusting for the Effect of Centre Group, Age, Sex, Baseline HAMD Mood Item Score and Duration of Current Episode of Depression
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR			Paroxetine IR			Placebo			Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(s.e.)	N	Mean	(95% C.I.)	p-value	Mean	(95% C.I.)	p-value
Baseline	2.7	(0.06)	103	2.8	(0.06)	103	2.7	(0.06)	107						
Week 2 LOCF	-0.6	(0.12)	103	-0.5	(0.12)	103	-0.4	(0.12)	107	-0.2	(-0.40, 0.08)	0.180	-0.1	(-0.30, 0.17)	0.576
Week 4 LOCF	-1.1	(0.14)	103	-1.0	(0.14)	103	-0.8	(0.14)	107	-0.3	(-0.56, -0.00)	0.048	-0.2	(-0.45, 0.10)	0.210
Week 6 LOCF	-1.2	(0.14)	103	-1.1	(0.14)	103	-0.8	(0.14)	107	-0.3	(-0.60, -0.07)	0.014	-0.3	(-0.54, -0.01)	0.039
Week 8 LOCF	-1.3	(0.14)	103	-1.2	(0.14)	103	-0.9	(0.14)	107	-0.4	(-0.63, -0.08)	0.013	-0.3	(-0.57, -0.02)	0.035
Week 10 LOCF	-1.4	(0.15)	103	-1.5	(0.15)	103	-0.9	(0.15)	107	-0.5	(-0.75, -0.18)	0.001	-0.6	(-0.85, -0.29)	<0.001
Week 12 LOCF	-1.4	(0.15)	103	-1.4	(0.15)	103	-0.9	(0.15)	107	-0.5	(-0.81, -0.22)	<0.001	-0.5	(-0.83, -0.26)	<0.001

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.487.CODE]LOCF1415.SAS (18NOV97 10:53)

Paroxetine CR - Protocol : 487

Figure 3.4.3

Cumulative Frequency Distribution
HAMD Mood Item Score
Change from Baseline at Endpoint

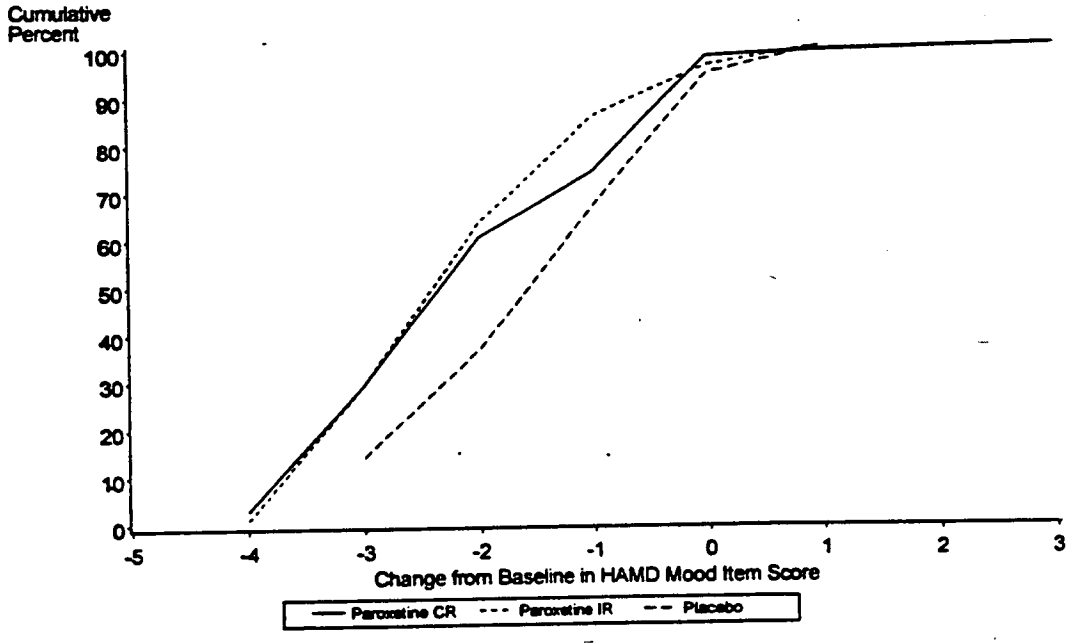

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Table 3.5.1.

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at All Time Points
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max) N	Median	(Min,Max) N	Median	(Min,Max) N	Median	(95% C.I.)	p-value	Median	(95% C.I.)	p-value
Baseline	4	103	4	103	4	106						
Week 1	0	102	0	102	0	105	0	(0.0, 0.0)	0.337	0	(0.0, 0.0)	0.801
Week 2	-1	99	0	94	0	97	0	(0.0, 0.0)	0.493	0	(0.0, 0.0)	0.975
Week 3	-1	90	-1	95	-1	90	0	(0.0, 0.0)	0.263	0	(0.0, 0.0)	0.504
Week 4	-1	93	-1	92	-1	96	0	(0.0, 0.0)	0.291	0	(0.0, 0.0)	0.603
Week 6	-1	86	-1	88	-1	93	0	(-1.0, 0.0)	0.012	0	(0.0, 0.0)	0.278
Week 8	-2	85	-1	82	-1	88	0	(-1.0, 0.0)	0.040	0	(0.0, 0.0)	0.441
Week 10	-2	83	-2	76	-1	88						
Week 12	-2	80	-2	73	-1	79	-1	(-1.0, 0.0)	<0.001	-1	(-1.0, 0.0)	0.004
Wk 12 End Point	-2	103	-2	103	-1	106	0	(-1.0, 0.0)	0.022	0	(-1.0, 0.0)	0.019

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.487.CODE]LT14_2.SAS (17NOV97 16:07)

Table 3.5.2

Baseline and Change from Baseline in CGI Severity of Illness Score
Statistical Analysis Presented at LOCF Endpoints
Intention to Treat Population

	Treatment Groups						Pairwise Comparisons					
	Paroxetine CR		Paroxetine IR		Placebo		Paroxetine CR vs Placebo			Paroxetine IR vs Placebo		
	Median	(Min,Max) N	Median	(Min,Max) N	Median	(Min,Max) N	Median	(95% C.I.)	p-value	Median	(95% C.I.)	p-value
Baseline	4	103	4	103	4	106						
Week 2 LOCF	-1	103	0	103	0	106	0	(0.0, 0.0)	0.371	0	(0.0, 0.0)	0.911
Week 4 LOCF	-1	103	-1	103	-1	106	0	(0.0, 0.0)	0.441	0	(0.0, 0.0)	0.582
Week 6 LOCF	-1	103	-1	103	-1	106	0	(-1.0, 0.0)	0.075	0	(0.0, 0.0)	0.404
Week 8 LOCF	-1	103	-1	103	-1	106	0	(-1.0, 0.0)	0.165	0	(0.0, 0.0)	0.650
Week 10 LOCF	-2	103	-2	103	-1	106	0	(-1.0, 0.0)	0.086	0	(-1.0, 0.0)	0.046
Week 12 LOCF	-2	103	-2	103	-1	106	0	(-1.0, 0.0)	0.022	0	(-1.0, 0.0)	0.019

Note: Only patients with a baseline and at least one post baseline assessment

DISK$STATS4:[STATS_GROUP.SBBRL29060.487.CODE]LOCF14_2.SAS (18NOV97 15:04)

Paroxetine CR - Protocol : 487
Figure 3.5.3
Cumulative Frequency Distribution
CGI Severity Score
Change from Baseline at Endpoint

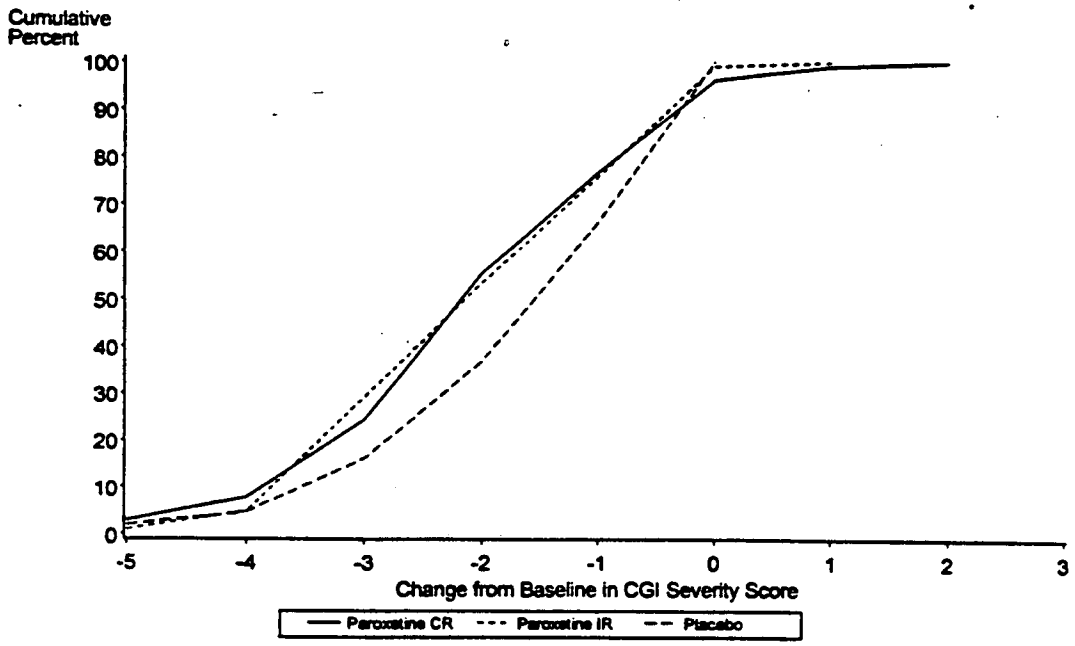

Figure 14.1.18.1 presents the cumulative frequency distribution of the change from baseline in HAMD total score. Both paroxetine CR and paroxetine IR had higher gradients than placebo. Figure 14.4.18.1 is similar to above, but this plots change from baseline in mood item score only. This plot shows much the same trend as figure 14.1.18.1. Figure 14.6.1.1 shows the cumulative frequency distribution of the change from baseline in CGI Severity score. Paroxetine CR and paroxetine IR again appear to have different gradients in comparison with placebo.