Study No.: 29060/810
Title: A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Efficacy and Safety of Paroxetine Controlled Release (12.5 and 25 mg/day) Versus Placebo in Patients with Major Depressive Disorder
Rationale: In two previous clinical trials, controlled-release (CR) paroxetine demonstrated antidepressant efficacy in the dosage range of 25 mg to 62.5 mg daily (paroxetine studies 448 and 449). In a clinical trial treating only subjects aged 60 years or older, paroxetine CR demonstrated antidepressant efficacy in the dosage range of 12.5 mg to 50 mg daily (paroxetine study 487). Prior to the initiation of the current trial, studies evaluating the antidepressant efficacy and the safety of fixed daily doses of paroxetine CR (i.e., 12.5 mg and 25 mg) have not been completed and reported , nor had the minimum effective daily dosage of paroxetine CR for the treatment of major depressive disorder (MDD) in adults been established. This study was designed to evaluate the efficacy and tolerability of paroxetine CR 12.5 mg and 25 mg daily.
Phase: IV
Study Period: 04 August 2001 - 19 March 2002
Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, parallel group study evaluating the efficacy and safety of paroxetine CR (12.5 mg/day and 25 mg/day) compared with placebo in the treatment of MDD.
Centers: 40 in USA
Indication: Major depressive disorder
Treatment: (# denotes treatment regimens approved in the US and at least one country in the European Union) Following an initial screening visit, subjects fulfilling the study inclusion and exclusion criteria entered a one-week, single-blind placebo run-in phase to further evaluate their suitability for entry into the study. Eligible subjects were randomized at the baseline visit to either paroxetine CR 12.5 mg/day, 25 mg/day#, or placebo (1:1:1 ratio) for an 8-week, double-blind treatment phase. All subjects at the Week 8 or early withdrawal visit were scheduled to return for a mandatory safety follow-up visit that was scheduled to occur 14 days following the discontinuation of study medication. Subjects with an ongoing adverse event at the 14-day safety follow-up visit were scheduled to return for another safety follow-up visit within 28 days.
Objective: The primary objective of this study was to evaluate the antidepressant efficacy of daily doses of paroxetine CR 12.5 mg and 25 mg versus placebo in the treatment of MDD. The secondary objective of the study was to descriptively examine the tolerability profile of paroxetine CR 12.5 mg daily versus paroxetine CR 25 mg daily and placebo.
Primary Outcome/Efficacy Variable: The primary efficacy variable was the change from baseline to study endpoint (Week 8 last observation carried forward [LOCF]) in the 17-item Hamilton Rating Scale for Depression (HAM-D).
Secondary Outcome/Efficacy Variables: The secondary efficacy variables were the change from baseline at study endpoint in HAM-D item 1 (depressed mood), the change from baseline in the clinical global impression (CGI) severity of illness score at study endpoint, the percentage of subjects with HAM-D total score ≤ 7 at study endpoint, the percentage of subjects with a CGI global improvement score of 1 or 2 at study endpoint, the change from baseline at study endpoint in the Sheehan Disability Scale (SDS) total and individual items (work, family, and social life), the change from baseline at study endpoint in the total score on the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and its individual items (the change from baseline at study endpoint in the physical health, work, social relationships, leisure time activities, living/housing situations, household activities, mood, overall sense of well being, and overall life satisfaction items on the Q-LES-Q, and satisfaction with medication at study endpoint in the Q-LES-Q). Safety was assessed via routine monitoring of adverse events as well as physical exam, vital signs, electrocardiogram (ECG) and laboratory assessments.
Statistical Methods: The primary treatment comparisons of interest were paroxetine CR arms (12.5 mg, and 25 mg/day) versus placebo for change from baseline in the HAM-D total score at Week 8 last observation carried forward (LOCF) in the intention-to-treat (ITT) population. All hypothesis tests and confidence intervals were two-sided. The main statistical tests were performed at the 5% level of significance. Continuous efficacy variables (e.g. change from baseline to study endpoint in the 17-item HAM-D total score) were analyzed using parametric analysis of covariance with results presented as point estimates, 95% confidence intervals (CIs), and associated p-values for the adjusted mean difference between treatments. For the primary variable, the treatment effect was to be considered statistically significant at the nominal 5% level and was adjusted for multiple comparisons using the Hochberg's modification to the Bonferroni inequality. Binary efficacy measures were analyzed using logistic regression with results presented as adjusted odds ratios, 95% CIs and associated p-values. Other categorical data (e.g., CGI Severity of Illness, Q-LES-Q individual items) were

analyzed using non-parametric methods with no adjustment for covariates.
For all analyses, primary inferences were obtained from the model adjusted for baseline efficacy measure (where applicable) and center grouping.
All adverse events (AEs) were listed. Descriptive statistics were employed to evaluate the incidence of AEs in treatment groups.

Study Population: Six hundred seventy six subjects were screened, 459 subjects were randomized, and 447 subjects (153 paroxetine CR 12.5 mg, 148 paroxetine CR 25 mg and 146 placebo) comprised the Intent to Treat (ITT) subject population. The following inclusion/exclusion criteria were employed to enroll subjects in this trial. Inclusion criteria were:

1. male or female subjects at least 18 years of age
2. primary diagnosis of MDD according to DSM-IV (296.2/296.3)
3. HAM-D 17-item total score of ≥20 at screen and baseline visits
4. HAM-D item 1 (depressed mood) score ≥2 at screen and baseline visits.
5. Subjects had to provide written informed consent before commencing any study-specific procedures.

Key exclusion criteria were:

1. subjects with a current (or within 6 months prior to screening) Axis I disorder other than MDD or with a history of schizophrenia, schizoaffective disorder, or bipolar disorder
2. subjects receiving formal psychotherapy concurrently or in the 12 weeks prior to the screen visit;
3. subjects who, in the investigator's judgement, posed a current serious suicidal or homicidal risk;
4. subjects with any serious medical disorder or condition that in the investigator's opinion precluded the administration of study medication
5. subjects who had taken monoamine oxidase inhibitors or fluoxetine within 4 weeks of the start of this trial or other antidepressants, sedatives, hypnotics, beta adrenergic blockers, benzodiazepines, or other psychoactive medications within 2 weeks of this trial
6. subjects who had taken depot neuroleptics within 12 weeks of the start of this trial
7. women who had a positive pregnancy test at the screen visit or who were lactating or planning to become pregnant within the course of the trial or women of child-bearing potential who were not practicing a clinically accepted method of contraception such as oral contraception.

Number of Subjects:	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Planned, N	146	146	146
Randomized, N	149	156	154
ITT Population, N	146	153	148
(Percentages below based on ITT)			
Completed, n (%)	113 (77.4)	127 (83.0)	110 (74.3)
Total Number Subjects Withdrawn, N (%)	33 (22.6)	26 (17.0)	38 (25.7)
Withdrawn Due to Adverse Events, n (%)	6 (4.1)	1 (0.7)	10 (6.8)
Withdrawn Due to Lack of Efficacy, n (%)	8 (5.5)	2 (1.3)	5 (3.4)
Withdrawn for Other Reasons, n (%)	19 (13.0)	23 (15.0)	23 (15.5)
Demographics (ITT Population)	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N	146	153	148
Females:Males	90:56	83:70	88:60
Mean Age, Years (SD)	38.4 (11.7)	38.6 (12.1)	39.4 (10.8)
White, n (%)	108 (74.0)	117 (76.5)	113 (76.4)
Age <65 Years, n (%)	144 (98.6)	152 (99.3)	146 (98.6)
Age ≥65 Years, n (%)	2 (1.4)	1 (0.7)	2 (1.4)

Primary Efficacy Results for ITT Population:			
HAM-D Total Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	146	153	148
Baseline, Raw Mean (SE)	23.8 (3.2)	23.2 (2.9)	23.5 (3.3)
N for Week 8 LOCF	142	151	143
Change to Week 8 LOCF, Least-Square (LS) Mean (SE)	-10.0 (0.60)	-11.7 (0.58)	-12.4 (0.60)
Week 8 LOCF Difference in Adjusted LS Means Between Paroxetine CR and Placebo		-1.7	-2.4
Week 8 LOCF Adjusted 95% CI for Difference Between Treatments		-3.38, -0.09	-4.06, -0.74
Week 8 LOCF p-Value for Difference Between Treatments		0.038	0.005
Secondary Efficacy Results for ITT Population:			
HAM-D Depressed Mood Item Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	146	153	148
Baseline, Median	3.0	3.0	3.0
N for Week 8 LOCF	142	151	143
Change to Week 8 LOCF, Median	-1.0	-1.0	-2.0
Wilcoxon Z Score for Week 8 LOCF Treatment Comparison		-1.1	-2.1
CGI Severity of Illness	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	146	153	148
Baseline, Median	4.0	4.0	4.0
N for Week 8 LOCF	142	151	144
Change to Week 8 LOCF, Median	-1.0	-1.0	-2.0
Wilcoxon Z Score for Week 8 LOCF Treatment Comparison		-2.1	-3.5
HAM-D Remitters (HAM-D </=7)	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Week 8 LOCF	142	151	143
Remitters for Week 8 LOCF, n (%)	37 (26.1)	51 (33.8)	58 (40.6)
Week 8 LOCF Adjusted Odds Ratio for Difference Between Treatments		1.38	1.96
Week 8 LOCF 95% CI for Adjusted Odds Ratio		0.81, 2.35	1.15, 3.33
Responders on the CGI Improvement Scale (CGI = 1 or 2)	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Week 8 LOCF	142	151	144
Responders for Week 8 LOCF, n (%)	72 (50.7)	82 (54.3)	91 (63.2)
Week 8 LOCF Adjusted Odds Ratio for Difference Between Treatments		1.17	1.68
Week 8 LOCF 95% CI for Adjusted Odds Ratio		0.73, 1.88	1.04, 2.73

SDS Total Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	142	150	148
Baseline, Raw Mean (SD)	17.2 (6.2)	16.9 (6.4)	17.5 (5.9)
N for Week 8 LOCF	131	141	135
Change to Week 8 LOCF, LS Mean (SE)	-4.2 (0.60)	-4.8 (0.58)	-5.5 (0.60)
Week 8 LOCF Difference in Adjusted LS Means Between Paroxetine CR and Placebo		-0.64	-1.32
Week 8 LOCF 95% CI for Difference Between Treatments		-2.29, 1.00	-2.99, 0.35
SDS Work Item Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	142	150	148
Baseline, Raw Mean (SD)	5.2 (2.4)	5.0 (2.8)	5.3 (2.7)
N for Week 8 LOCF	131	141	135
Change to Week 8 LOCF, LS Mean (SE)	-1.1 (0.22)	-1.1 (0.21)	-1.4 (0.22)
Week 8 LOCF Difference in Adjusted LS Means Between Paroxetine CR and Placebo		0.00	-0.32
Week 8 LOCF 95% CI for Difference Between Treatments		-0.61, 0.60	-0.93, 0.30
SDS Social Life Item Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	146	153	148
Baseline, Raw Mean (SD)	6.2 (2.6)	6.1 (2.6)	6.3 (2.2)
N for Week 8 LOCF	135	144	135
Change to Week 8 LOCF, LS Mean (SE)	-1.6 (0.23)	-1.9 (0.22)	-2.1 (0.23)
Week 8 LOCF Difference in Adjusted LS Means Between Paroxetine CR and Placebo		-0.24	-0.53
Week 8 LOCF 95% CI for Difference Between Treatments		-0.86, 0.37	-1.16, 0.10
SDS Family Life Item Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	146	153	148
Baseline, Raw Mean (SD)	5.8 (2.6)	5.7 (2.3)	5.9 (2.4)
N for Week 8 LOCF	135	144	135
Change to Week 8 LOCF, LS Mean (SE)	-1.5 (0.21)	-1.9 (0.21)	-1.9 (0.21)
Week 8 LOCF Difference in Adjusted LS Means Between Paroxetine CR and Placebo		-0.45	-0.39
Week 8 LOCF 95% CI for Difference Between Treatments		-1.04, 0.13	-0.98, 0.21
Q-LES-Q Total Score	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N for Baseline	146	153	148
Baseline, Raw Mean (SD)	47.0 (14.8)	48.3 (13.1)	47.5 (12.7)
N for Week 8 LOCF	129	131	127
Change to Week 8 LOCF, LS Mean (SE)	8.2 (1.41)	11.9 (1.40)	12.3 (1.44)
Week 8 LOCF Difference in Adjusted LS Means Between Paroxetine CR and Placebo		3.68	4.10
Week 8 LOCF 95% CI for Difference Between Treatments		-0.22, 7.58	0.17, 8.03
Q-LES-Q Physical Health Item (note: positive Wilcoxon Z score indicates a favorable treatment response)	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		-0.4	0.3

Q-LES-Q Work Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		1.5	2.1
Q-LES-Q Social Relationships Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		0.7	0.4
Q-LES-Q Leisure Time Activities Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		0.6	1.2
Q-LES-Q Living/Housing Situations Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		1.5	2.0
Q-LES-Q Household Activities Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		1.8	1.0
Q-LES-Q Mood Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		1.4	2.4
Q-LES-Q Overall Well-Being Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		1.4	1.9
Q-LES-Q Overall Life Satisfaction Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		1.7	1.8
Q-LES-Q Satisfaction with Medication Item	**Placebo**	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Wilcoxon Z Score for Week 8 LOCF Paroxetine CR vs. Placebo		-0.1	0.4

Safety Results for ITT Population: On-therapy adverse events (AEs) were defined as all AEs where the onset date was on or after the first day of treatment and before or on the last day of treatment. All serious adverse events (SAEs) are presented including those occurring within 30 days of the end of treatment.

	Placebo	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
Most Frequent Adverse Events for ITT Population – On-Therapy			
N	146	153	148
	n (%)	**n (%)**	**n (%)**
Subjects with any AE(s), n (%)	111 (76.0)	120 (78.4)	118 (79.7)
Headache	31 (21.2)	38 (24.8)	30 (20.3)
Respiratory Disorder	17 (11.6)	28 (18.3)	26 (17.6)
Dry Mouth	14 (9.6)	20 (13.1)	22 (14.9)
Diarrhea	13 (8.9)	21 (13.7)	21 (14.2)
Nausea	13 (8.9)	13 (8.5)	18 (12.2)
Somnolence	9 (6.2)	13 (8.5)	15 (10.1)
Dizziness	8 (5.5)	7 (4.6)	15 (10.1)
Abnormal Ejaculation (corrected for gender)	2 (3.6)	4 (5.7)	6 (10.0)
Dyspepsia	10 (6.8)	13 (8.5)	14 (9.5)
Abdominal Pain	6 (4.1)	6 (3.9)	13 (8.8)
Insomnia	9 (6.2)	16 (10.5)	8 (5.4)
Trauma	3 (2.1)	10 (6.5)	7 (4.7)
Sweating	1 (0.7)	10 (6.5)	6 (4.1)
Libido Decreased	4 (2.7)	12 (7.8)	4 (2.7)
Infection	4 (2.7)	10 (6.5)	4 (2.7)
Sinusitis	9 (6.2)	7 (4.6)	3 (2.0)

Gender Non-Specific Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	Placebo	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N	146	153	148
Subjects with Non-Fatal SAEs, n (%)	3 (2.1)	3 (2.0)	4 (2.7)
	n (%) [related]	**n (%) [related]**	**n(%) [related]**
Abnormal Laboratory Value	0	2 (1.3) [0]	1 (0.7) [0]
Gall Bladder Disorder	0	0	1 (0.7) [0]
Anxiety	0	0	1 (0.7) [0]
Emotional Lability	0	0	1 (0.7) [0]
Cerebrovascular Disorder	1 (0.7) [0]	0	0
Depression	1 (0.7) [0]	0	0
Bronchitis	1 (0.7) [0]	0	0
Carcinoma of the Lung	0	1 (0.7) [0]	0
Pleura Disorder	1 (0.7) [0]	0	0
Sinusitis	1 (0.7) [0]	0	0
Subjects with Fatal SAEs, n (%)	0	0	0

Female-Specific Serious Adverse Events - On-Therapy
n (%) [n considered by the investigator to be related to study medication]

	Placebo	**Paroxetine CR 12.5 mg**	**Paroxetine CR 25 mg**
N	90	83	88
Subjects with Non-Fatal SAEs, n (%)	2 (2.2)	0	1 (1.1)
	n (%)[related]	**n (%) [related]**	**n (%)[related]**
Unintended Pregnancy	2 (2.2) [0]	0	1 (1.1) [0]
Subjects with Fatal SAEs, n (%)	0	0	0

Conclusions: See publication below.

Publications:

Trivedi MH, Pigott TA, Perera P, Dillinangham K, Carfagno M, Pitts C:. Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. J Clin Psychiatry 2004;65:1356-1364.

Paroxetine cr efficacy and tolerability at low doses in the treatment of major depression. Trivedi, Mark 1, Dillingham, Kerry 2, and Pitts, Cornelius D 2 International Congress of the World Federation of Biological Psychiatry 2/9/2004 Sydney; Australia

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