Study No.: 29060/785
Title: A double-blind, placebo-controlled, fixed-dosage study comparing the efficacy and tolerability of paroxetine CR and citalopram to placebo in the treatment of Major Depressive Disorder with anxiety
Rationale: Paroxetine is a selective serotonin re-uptake inhibitor approved by regulatory authorities for the treatment of Major Depressive Disorder. Two formulations have been approved: an immediate-release (IR) formulation in 1991, and, more recently, a controlled-release (CR) formulation. For the CR formulation, efficacy has been established in the dosage range of 25 mg to 62.5 mg in the treatment of major depressive disorder (MDD). At the initiation of this trial, there were no fixed-dosage studies evaluating the efficacy of paroxetine CR; therefore, the primary objective of this trial was to assess the efficacy of fixed dosages of paroxetine CR relative to placebo. . Paroxetine CR 12.5 mg and 25mg daily were selected in order to provide specific data on the efficacy and safety associated with these lower doses of this paroxetine formulation. Citalopram hydrobromide is a racemic bicyclic phthalane derivative also demonstrating selective inhibition of neuronal serotonin re-uptake. This agent is indicated for the treatment of depression as established in 4-6 week controlled trials of outpatients diagnosed with depression according to DSM-III and DSM-III-R criteria (Package Insert, 2000). The Citalopram prescribing information states that dosing should begin at 20mg daily, generally with an increase to 40mg daily (Package Insert, 2000). However, fixed dose placebo controlled trials failed to establish the relationship between dose and therapeutic benefit for citalopram. Therefore, as a secondary objective in this study citalopram 20mg and 40mg daily were included to provide efficacy and tolerability information specifically associated with these doses.
Phase: IV
Study Period: 11 April 2001 - 29 August 2001
Study Design: This was a multicenter, double-blind, placebo-controlled, parallel-group, randomized study with a six-week treatment duration.
Centers: This study was conducted by investigators at 40 centers in the USA.
Indication: Major depressive disorder with anxiety
Treatment:(# Denotes treatment regimens approved in the US and at least one country in the European Union.) Paroxetine CR and citalopram were provided as over-encapsulated tablets. Paroxetine CR was provided in 12.5 and 25 mg strengths, while citalopram was provided in 10, 20, 30, and 40 mg strengths. Placebo capsules were identical in appearance to the active study medication capsules. Subjects were randomized (1:1:1:1:1) to either paroxetine CR 12.5 mg, paroxetine CR 25 mg#, citalopram 20 mg#, citalopram 40 mg#, or placebo. For the first week of treatment, the beginning dosage for paroxetine CR-treated subjects was 12.5 mg and 10 mg for citalopram-treated subjects. Subjects in the paroxetine CR 25 mg and both citalopram treatment groups were titrated after one week to 25 mg and 20 mg, respectively. Subjects randomized to the citalopram 40 mg treatment group were titrated to 30 mg after week two and to 40 mg of citalopram after week three. Subjects randomized to placebo remained on placebo throughout the study.
Objective: The primary objective of this study was to compare the efficacy of 25 mg paroxetine CR to placebo and 12.5 mg paroxetine CR to placebo in the treatment of MDD with anxiety. The secondary objectives of this study were: 1) to compare the efficacy of 20 mg and 40 mg citalopram to placebo.;2) to assess the relationship between dosage and efficacy of paroxetine CR and citalopram; 3) to assess the safety and tolerability of paroxetine CR and citalopram in the treatment of Major Depressive Disorder with anxiety.
Primary Outcome/Efficacy Variable: The primary efficacy measure defined by the protocol was the proportion of Montgomery and Asberg Depression Rating Scale (MADRS) responders at the week 6 last observation carried forward (LOCF) endpoint. Response was defined as a reduction of 50% or more in the MADRS total score, relative to the baseline total score.
Secondary Outcome/Efficacy Variables: Secondary efficacy measures included the mean change from baseline in the MADRS total score; the proportion of subjects with a positive response (score of 1 or 2) on the Global Improvement rating of the Clinical Global Impression (CGI); the mean change from baseline in CGI severity of illness rating; the mean change from baseline in the Hamilton Anxiety Rating Scale (HAM-A) total score; the mean change from baseline in Hospital Anxiety and Depression Scale (HAD) total score; the mean change from baseline in HAD, Anxiety, and Depression subscales; and the mean change from baseline in Sheehan Disability Scale (SDS) total score. Safety was assessed via adverse event monitoring, vital signs, laboratory evaluation, serum pregnancy test, ECGs, physical exam and weight
Statistical Methods: All subjects who were randomized to double-blind medication and had at least one valid post-baseline efficacy assessment comprised the intent-to-treat (ITT) efficacy population. The LOCF data at week 6 were the primary dataset of interest. The first planned primary comparison of paroxetine CR 25 mg versus placebo was tested at a significance level of 0.05. If this was significant, the second planned primary comparison of paroxetine CR 12.5 mg versus placebo was based on a two-sided hypothesis at a type I error rate of 0.05. If the first comparison was not significant, no further inferential testing was to be done. Main effects in the model were assessed at 5% level of significance. The primary

measure to assess efficacy (i.e., proportion of MADRS responders) and other binary efficacy variables were analyzed by logistic analysis model with treatment and region. Continuous efficacy variables were analyzed by analysis of variance (ANOVA) models with treatment and region effects.

Study Population: Four hundred and ninety-six outpatients (placebo, 102; paroxetine CR 12.5 mg, 94; paroxetine CR 25 mg, 98; citalopram 20 mg, 105; citalopram 40 mg, 97) comprised the intention-to-treat (ITT) safety population. The following key inclusion/exclusion criteria were employed to enrol subjects in this trial:

Inclusion was based on:

1. Subjects were males or females between the ages of 18 and 65
2. Subjects had a Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) diagnosis of Major Depressive Disorder
3. Subjects had a MADRS score of at least 20 and a HAM-A score of at least 17 (both at the screening and baseline visits).
4. Subjects were required to provide written informed consent prior to any study-specific procedures.

The following subjects were *excluded* from the study:

1. Subjects who had taken other psychotropic drugs must have discontinued these prior to baseline. The minimum discontinuation periods were 5 half-lives for hypnotics, benzodiazepines, all other sedatives, tricyclic antidepressants (TCAs), selective norepinephrine re-uptake inhibitors (SNRIs), serotonin re-uptake inhibitors (SSRIs) other than fluoxetine, lithium and oral neuroleptics, or herbal psychoactive medications (e.g., St. John's Wort); 4 weeks for fluoxetine and monoamine oxidase inhibitors (MAOIs); and 12 weeks for depot neuroleptics.
2. Subjects who had a history of schizophrenia or schizoaffective disorder.
3. Subjects who had current (or within 6 months prior to screening) Axis I anxiety disorder or Axis I affective disorder other than Major Depressive Disorder.
4. Subjects who, in the investigator's judgement, posed a current homicidal or suicidal risk
5. Woman who had a positive pregnancy test or who were lactating, women of child-bearing potential who were not practicing a clinically accepted method of contraception .
6. Subjects with any serious medical disorder or condition that, in the investigator's opinion, precluded the administration of paroxetine CR or citalopram.
7. Subjects undergoing any form of psychotherapy.

Number of Subjects:	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
Randomized N	105	103	96	107	100
Intention-to-Treat (ITT, safety) N	102	98	94	105	97
(Percentages below based on ITT)					
Completed, n (%)	87 (85.3)	80 (81.6)	78 (83)	90 (85.7)	74 (76.3)
Total Number Subjects Withdrawn, N (%)	15 (14.7)	18 (18.4)	16 (17.0)	15 (14.3)	23 (23.7)
Withdrawn Due to Adverse Events, n (%)	2 (2.0)	9 (9.2)	2 (2.1)	5 (4.8)	5 (5.2)
Withdrawn Due to Lack of Efficacy, n (%)	1 (1.0)	1 (1.0)	4 (4.3)	2 (1.9)	1 (1.0)
Withdrawn for Other Reasons, n (%)	12 (11.8)	8 (8.2)	10 (10.6)	8 (7.5)	17 (17.5)
Demographics	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N (ITT, safety)	102	98	94	105	97
Females:Males	57:45	61:37	57:37	58:47	57:40
Mean Age, Years (SD)	40.2 (11.5)	41.5 (12.1)	41.2 (12.3)	38.4 (11.3)	39.6 (11.1)
White, n (%)	77 (75.5)	75 (76.5)	67 (71.3)	80 (76.2)	70 (72.2)
Primary Efficacy Results for ITT Population:					
MADRS Responder Analysis	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
ITT N (efficacy)	101	97	93	104	95
Total Responders at Week 6 LOCF Endpoint, n (%)	36 (35.6)	43 (44.3)	34 (36.6)	54 (51.9)	48 (50.5)
Odds Ratio		1.47	1.04	1.97	1.88
95% CI		0.83, 2.60	0.58, 1.88	1.13, 3.46	1.06, 3.35
p-Value		0.191	0.887	0.018	0.031

Secondary Efficacy Results:					
MADRS Total Score	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	101	97	93	104	95
Baseline, Mean (SE)	31.7 (0.5)	31.4 (0.5)	31.7 (0.5)	31.4 (0.5)	31.0 (0.5)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-12.1 (1.1)	-13.8 (1.1)	-11.9 (1.1)	-15.0 (1.0)	-15.3 (1.1)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-1.7	0.1	-2.9	-3.2
95% CI		-4.67, 1.20	-2.82, 3.11	-5.76, 0.00	-6.20, -0.30
CGI Global Improvement Item Responder Analysis	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	101	97	93	104	95
Total Responders at Week 6 LOCF Endpoint, n (%)	42 (41.6)	54 (55.7)	43 (46.2)	61 (58.7)	55 (57.9)
Odds Ratio		1.86	1.21	2.04	2.03
95% CI		1.05, 3.29	0.68, 2.15	1.16, 3.58	1.14, 3.60
CGI Severity of Illness Score	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	101	97	93	104	95
Baseline, Mean (SE)	4.5 (0.1)	4.6 (0.1)	4.6 (0.1)	4.5 (0.1)	4.5 (0.1)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-1.2 (0.1)	-1.5 (0.1)	-1.2 (0.1)	-1.5 (0.1)	-1.6 (0.1)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-0.3	0.0	-0.3	-0.4
95% CI		-0.63, 0.08	-0.35, 0.36	-0.66, 0.03	-0.79, -0.07
HAM-A Total Score	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	101	97	93	104	95
Baseline, Mean (SE)	23.4 (0.4)	23.0 (0.4)	23.3 (0.5)	23.4 (0.4)	23.6 (0.4)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-9.2 (0.8)	-9.8 (0.8)	-8.8 (0.8)	-10.8 (0.8)	-11.3 (0.8)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-0.6	0.4	-1.6	-2.1
95% CI		-2.76, 1.55	-1.82, 2.53	-3.70, 0.53	-4.27, 0.06
HAD Total Score	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	101	96	93	104	95
Baseline, Mean (SE)	24.9 (0.6)	25.7 (0.6)	24.6 (0.6)	25.4 (0.6)	24.8 (0.6)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-6.8 (0.8)	-9.4 (0.8)	-7.9 (0.9)	-10.3 (0.8)	-10.2 (0.8)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-2.5	-1.1	-3.4	-3.4
95% CI		-4.83, -0.25	-3.41, 1.20	-5.68, -1.20	-5.68, -1.09

HAD Anxiety Subscale Score	Placebo	Paroxetine CR 25 mg	Paroxetine CR 12.5 mg	Citalopram 20 mg	Citalopram 40 mg
N for Baseline	101	96	93	104	95
Baseline, Mean (SE)	12.9 (0.3)	13.4 (0.4)	13.4 (0.4)	13.0 (0.3)	13.0 (0.4)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-3.7 (0.4)	-5.2 (0.5)	-4.6 (0.5)	-5.1 (0.4)	-5.4 (0.5)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-1.5	-1.0	-1.4	-1.7
95% CI		-2.78, -0.28	-2.24, 0.28	-2.65, -0.21	-2.95, -0.45
HAD Depression Subscale Score	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	101	96	93	104	95
Baseline, Mean (SE)	12.0 (0.4)	12.3 (0.4)	11.1 (0.4)	12.4 (0.4)	11.8 (0.4)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-3.2 (0.5)	-4.2 (0.5)	-3.3 (0.5)	-5.2 (0.5)	-4.8 (0.5)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-1.0	-0.1	-2.0	-1.7
95% CI		-2.30, 0.28	-1.43, 1.17	-3.27, -0.74	-2.98, -0.39
SDS Total Score	**Placebo**	**Paroxetine CR 25 mg**	**Paroxetine CR 12.5 mg**	**Citalopram 20 mg**	**Citalopram 40 mg**
N	98	87	89	97	86
Baseline, Mean (SE)	19.7 (0.5)	20.3 (0.6)	19.2 (0.6)	20.2 (0.5)	18.4 (0.6)
Change from Baseline to Week 6 LOCF Endpoint, Mean (SE)	-4.9 (0.7)	-5.8 (0.8)	-5.1 (0.8)	-7.3 (0.7)	-7.4 (0.8)
Difference from Placebo in Change from Baseline at Week 6 LOCF Endpoint, Mean (SE)		-0.8	-0.2	-2.4	-2.4
95% CI		-2.92, 1.31	-2.28, 1.92	-4.45, -0.35	-4.53, -0.30

Safety Results: 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 SAEs are presented including those occurring within 30 days of the end of treatment.

Most Frequent Adverse Events for ITT Safety Population – On-Therapy	Placebo	Paroxetine CR 25 mg	Paroxetine CR 12.5 mg	Citalopram 20 mg	Citalopram 40 mg
ITT safety N	102	98	94	105	97
Subjects with any AE(s), n (%)	79 (77.5)	81 (82.7)	73 (77.7)	91 (86.7)	79 (81.4)
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Headache	20 (19.6)	22 (22.4)	22 (23.4)	30 (28.6)	24 (24.7)
Dry Mouth	11 (10.8)	19 (19.4)	10 (10.6)	20 (19.0)	11 (11.3)
Abnormal Ejaculation[1] (corrected for gender)	1 (2.2)	7 (18.9)	4 (10.8)	9 (19.1)	4 (10.0)
Diarrhea	6 (5.9)	16 (16.3)	13 (13.8)	10 (9.5)	13 (13.4)
Nausea	8 (7.8)	14 (14.3)	16 (17.0)	19 (18.1)	16 (16.5)
Somnolence	9 (8.8)	14 (14.3)	8 (8.5)	15 (14.3)	20 (20.6)
Insomnia	9 (8.8)	13 (13.3)	17 (18.1)	19 (18.1)	10 (10.3)
Asthenia	5 (4.9)	12 (12.2)	10 (10.6)	12 (11.4)	14 (14.4)
ITT safety N	102	98	94	105	97
Subjects with Non-Fatal SAEs, n (%) [n considered by the investigator to be related to study medication]	6 (5.9)	3 (3.1)	1 (1.1)	6 (5.7)]	2 (2.1)
	n (%) related]	**n (%) related]**	**n (%) related]**	**n (%) [related]**	**n (%) related]**
Abnormal Laboratory Value	4 (3.9) [2]	3 (3.1) [1]	1 (1.1) [1]	5 (4.8) [2]	1 (1.0) [0]
Gastrointestinal Disorder	1 (1.0) [0]	0	0	0	0
Myocardial Infarction	1 (1.0) [0]	0	0	0	0

Syncope	0	0	0	1 (1.0) [0]	0
Emotional Lability	0	1 (1.0) [0]	0	0	1 (1.0) [0]
Subjects with Fatal SAEs, n (%) * Suicide	1 (1.0)* [0] 1 (1.0) [0]	0	0	0	0

Conclusion:
Based on the primary efficacy variable, this study did not show statistical superiority of two fixed doses of paroxetine CR (12.5 and 25 mg) to placebo in treating subjects with major depressive disorder and anxiety in this 6 week trial. The results of the secondary efficacy analyses indicate that citalopram 20 mg and 40 mg were statistically superior to placebo in the proportion of MADRS responders at the week 6 LOCF endpoint.

Publications:

A double-blind comparison of citalopram and paroxetine in the treatment of patients with depression and anxiety. James Jefferson, John Griest American College of Neuropsychopharmacology 39th Annual Meeting 12/11/2000 San Juan; Puerto Rico

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