Study No.: 29060/448

Title: A Double-Blind, Placebo Controlled Trial to Evaluate the Clinical Effects of Immediate Release Paroxetine and Modified Release Paroxetine in the Treatment of Major Depression

Rationale: Paroxetine (BRL 29060) is a selective serotonin re-uptake inhibitor (SSRI). The Immediate Release (IR) formulation of this compound is FDA approved for use in the treatment of major depressive disorder (MDD). Paroxetine is generally well tolerated, with nausea, headache, sweating and somnolence being the most frequently reported adverse events (AE). These effects are usually transient and mild, but nonetheless may result in reduced treatment compliance or discontinuation of therapy in depression. Treatment failure consequent to reduced compliance or therapy discontinuation may be associated with compromised quality of life. Thus, by reducing the frequency of adverse events, subjects may be better able to sustain activities associated with daily living, as well as realize an improvement in clinical outcomes. In developing the Controlled Release (CR) formulation, data from a volunteer study showed reduced C_{max} and increased T_{max} for an enteric coated dosage form. Results from an additional volunteer trial suggested that this alteration in the pharmacokinetic profile may result in improved paroxetine tolerability, which in turn may enhance treatment compliance and the likelihood of treatment success.

Phase: III

Study Period: 4 September 1996 - 19 June 1997

Study Design: 12-week, multicenter, double-blind, randomized, placebo-controlled study.

Centres: Twenty centres in the United States.

Indication: Major Depressive Disorder

Treatment: # Denotes treatment regimens approved in the US and at least one country in the European Union.
A single-blind placebo (PBO) pre-treatment period was used to screen potential candidates for inclusion in the study. Those determined to be eligible following the one-week run-in phase were randomized to receive 12 weeks of study medication at the baseline visit. Subjects were distributed evenly to CR, IR, and PBO groups. The dosage range for CR was 25 to 62.5 mg daily# and for IR, from 20 to 50 mg daily#. Blinding of study medication was maintained by referring to dosage levels 1 through 4 (25 mg/20 mg = level 1, 37.5 mg/30 mg = level 2, 50 mg/40 mg = level 3, 62.5 mg/50 mg = level 4).
This study used a flexible dosage scheme. Randomized patients were initiated at therapy level 1. Dosage elevations were permitted if the subject's therapeutic response was inadequate as determined by the investigator's clinical judgment. Increases in daily dosage were prescribed at clinic visits only and were not permitted between visits. Such elevations were made at the rate of one dosage level/week (12.5 and 10 mg/day for CR and IR, respectively). However, dosage reductions to the next lowest level consequent to an AE were permitted at any time after the Week 1 visit. Patients requiring a dosage reduction prior to the Week 1 visit could interrupt treatment for a maximum of 2 days. Longer treatment interruptions required termination from the study. Patients requiring more than one dosage reduction were also discontinued from the study. Subjects were permitted to return to the original dose upon resolution of AEs. Gradual reduction of dosage was undertaken for subjects who completed the trial or who prematurely withdraw (if appropriate). This taper period lasted up to 10 days.

Objectives: The primary objective of this study was to evaluate the efficacy of paroxetine CR in the treatment of major depression. The secondary objective was to demonstrate the safety of paroxetine CR in the treatment of major depression, and to compare, through descriptive listings, the tolerability of paroxetine CR with the IR formulation relative to PBO.

Primary Outcome/Efficacy Variable: Primary efficacy was measured by the mean change from baseline to study end point in the total score on the 17-item Hamilton Depression Scale (HAMD-17).

Secondary Outcome/Efficacy Variable(s): Secondary efficacy was determined at study endpoint for:
1. Proportion of responders as determined by Clinical Global Impressions (CGI), global improvement item (score of 1 or 2).
2. Change from baseline to study endpoint in the Clinical Global Impressions (CGI), severity of illness item.
3. Proportion of responders as determined by a HAMD-17 total score ≤8.
4. Change from baseline in the depressed mood item 1 of the HAMD-17.
5. Change from baseline in the anxiety factor sub-score of the HAMD-17 (items 10, 11, 12, 13, 15, and 17).
6. Change from baseline in the sleep disturbance factor sub-score of the HAMD-17 (items 4, 5, 6).
7. The following Quality of Life parameters were also evaluated as secondary efficacy parameters:
    a. Change from baseline to the Week 12 LOCF endpoint in the physical health, subjective feelings, leisure time activities, social relationships, and general activities subscales.
    b. Overall life satisfaction at the Week 12 LOCF endpoint.
    c. Satisfaction with medication at the Week 12 LOCF endpoint.

Statistical Methods: All subjects receiving study medication with at least one safety assessment were assessed for clinical safety and tolerability. All subjects who received at least one dose of study medication and had at least one post-baseline assessment were included in the Intent-to-Treat (ITT) analyses. Primary inferences concerning the efficacy of paroxetine

were made using the last observation carried forward dataset (LOCF) of the ITT population, defined as the last on-drug assessment.
All hypothesis tests were two-sided. Interactions were significant at 10%, all others at 5 % level of significance. Continuous efficacy variables were analyzed by analysis of variance techniques with results presented as point estimates and 95 % confidence intervals (CIs) for the differences. Ordered contingency tables were analyzed using the Wilcoxon midrank sum test. Categorical data were analyzed using logistic regression with results presented as odds-ratios and 95% CIs around the odds-ratios. No statistical comparisons were made between paroxetine CR and IR.

Study Population: Three hundred ten out-patients (CR, 104; IR, 105; placebo, 101) aged 18 to 65 years diagnosed with MDD comprised the ITT population.

To be eligible, subjects had to meet the following inclusion criteria at the screening and/or baseline visits:

1. An out-patient with a primary diagnosis of MDD using the Structured Clinical Interview (SCID).
2. At least 18 years old and not older than 65 years of age.
3. A HAMD-17 total score of > 20 (the HAMD-17 total score could not have decreased more than 25% between the screening and baseline visits).
4. Written informed consent.

Key exclusion criteria:

1. Patients diagnosed with an Axis I disorder as a primary or dominant diagnosis within 6 months prior to the screening visit.
2. Patients with a history of brief depressive episodes
3. Women with a positive pregnancy test or who were lactating.
4. Women of child-bearing potential who were not practicing a clinically accepted method of contraception
5. Patients who, in the investigator's judgment posed a current, serious suicidal or homicidal risk.
6. Patients who had taken other psychotropic drugs or antidepressants within 14 days of baseline or depot-neuroleptics within 12 weeks.
7. Patients undergoing formal psychotherapy/psychoanalysis.

Number of Subjects:	**Paroxetine CR**	**Paroxetine IR**	**PBO**
Randomized, N	106	106	103
(Percentages below are based on ITT)			
Completed, n (%)	72 (69.2)	70 (66.7)	74 (73.3)
Total Number Subjects Withdrawn, N (%)	32 (30.8)	35 (33.3)	27 (26.7)
Withdrawn due to Adverse Events, n (%)	13 (12.5)	16 (14.3)	6 (5.9)
Withdrawn due to Lack of Efficacy, n (%)	3 (2.9)	6 (5.7)	10 (9.9)
Withdrawn for other reasons, n (%)	16 (15.4)	13 (12.4)	11 (10.9)

Demographics:	**Paroxetine CR**	**Paroxetine IR**	**PBO**
N (ITT)	104	105	101
Females: Males	62:42	67:38	67:34
Mean Age, years (SD)	38.9 (10.64)	39.4 (10.65)	38.7 (9.91)
White, n (%)	95 (91.35)	94 (89.52)	86 (85.15)

Primary Efficacy Results:

Baseline and Change from Baseline in HAMD-17 Total Score

	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N*	Mean	SE	N*	Mean	SE	N
Baseline	23.0	0.26	102	23.3	0.28	104	23.4	0.29	101
Change from Baseline at Week 12 LOCF Endpoint	-12.7	0.80	102	-11.1	0.81	104	-9.9	0.80	101

Comparison	**Paroxetine CR to Placebo**			**Paroxetine IR to Placebo**		
	Mean	95% CI	p	Mean	95% CI	p
Change from Baseline at Week 12 LOCF Endpoint	-2.8	-4.94, -0.59	0.013	-1.2	-3.40, 0.97	0.275

Secondary Outcome Variable(s):									
Proportion of HAMD-17 Responders (Total Score ≤ 8)									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	n	%	N	N	%	N	N	%	N
Week 12 LOCF Endpoint	49	48.0	102	45	43.3	104	38	37.6	101
Comparison	**Paroxetine CR to Placebo**				**Paroxetine IR to Placebo**				
	Odds Ratio		95% CI		Odds Ratio		95% CI		
Week 12 LOCF Endpoint	1.536		0.856, 2.757		1.321		0.731, 2.387		
Baseline and Change from Baseline in HAMD-17 Depressed Mood Item Score									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	2.8	0.06	102	2.9	0.06	104	2.9	0.06	101
Change from Baseline at Week 12 LOCF Endpoint	-1.8	0.19	102	-1.5	0.19	104	-1.2	0.19	101
Comparison	**Paroxetine CR to Placebo**				**Paroxetine IR to Placebo**				
	Mean		95% CI		Mean		95% CI		
Change from Baseline at Week 12 LOCF Endpoint	-0.6		-0.91, -0.26		-0.3		-0.65, -0.00		
Baseline and Change from Baseline in HAMD-17 Anxiety Factor Score									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	7.5	0.15	102	7.2	0.16	104	7.2	0.16	101
Change from Baseline at Week 12 LOCF Endpoint	-3.8	0.27	102	-3.4	0.27	104	-3.1	0.27	101
Comparison	**Paroxetine CR to Placebo**				**Paroxetine IR to Placebo**				
	Mean		95% CI		Mean		95% CI		
Change from Baseline at Week 12 LOCF Endpoint	-0.7		-1.41, 0.06		-0.3		-1.00, 0.47		
Baseline and Change from Baseline in HAMD-17 Sleep Disturbance Factor Score									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	3.3	0.16	102	3.5	0.16	104	3.7	0.16	101
Change from Baseline at Week 12 LOCF Endpoint	-1.8	0.16	102	-1.6	0.17	104	-1.5	0.17	101
Comparison	**Paroxetine CR to Placebo**				**Paroxetine IR to Placebo**				
	Mean		95% CI		Mean		95% CI		
Change from Baseline at Week 12 LOCF Endpoint	-0.2		-0.69, 0.21		-0.1		-0.55, 0.36		
Baseline and Change from Baseline in CGI-S Score									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Median	Min, Max	N	Median	Min, Max	N	Median	Min, Max	N
Baseline	4	3, 6	96	4	4, 6	102	4	3, 6	99
Change from Baseline at Week 12 LOCF Endpoint	-2	-4, 1	96	-1	-5, 1	100	-1	-4, 1	99
Proportion of CGI-I Responders (Score of 1 or 2)									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	n	%	N	N	%	N	N	%	N
Week 12 LOCF Endpoint	69	67.6	102	60	57.1	105	50	49.5	101
Comparison	**Paroxetine CR to Placebo**				**Paroxetine IR to Placebo**				
	Odds Ratio		95% CI		Odds Ratio		95% CI		
Week 12 LOCF Endpoint	2.206		1.214, 4.010		1.318		0.738, 2.354		
Baseline and Change in Baseline Q-LES-Q Physical Health Scores									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	43.2	1.50	92	46.3	1.63	92	45.1	1.73	95

Change from Baseline at Week 12 LOCF Endpoint	16.1	2.12	92	15.1	2.12	92	9.4	2.08	95
Comparison	**Paroxetine CR to Placebo**					**Paroxetine IR to Placebo**			
	Mean		95% CI			Mean		95% CI	
Change from Baseline at Week 12 LOCF Endpoint	6.7		0.89, 12.53			5.7		-0.11, 11.50	
Baseline and Change in Baseline Q-LES-Q Subjective Feelings Scores									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	49.0	1.20	92	46.3	1.34	92	47.2	1.63	95
Change from Baseline at Week 12 LOCF Endpoint	17.9	1.97	92	19.8	1.97	92	11.3	1.94	95
Comparison	**Paroxetine CR to Placebo**					**Paroxetine IR to Placebo**			
	Mean		95% CI			Mean		95% CI	
Change from Baseline at Week 12 LOCF Endpoint	6.6		1.18, 12.02			8.6		3.18, 13.99	
Baseline and Change in Baseline Q-LES-Q Leisure Time Activities Scores									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	50.4	1.83	91	48.6	2.17	92	46.3	2.00	95
Change from Baseline at Week 12 LOCF Endpoint	15.2	2.54	91	16.9	2.53	92	11.5	2.49	95
Comparison	**Paroxetine CR to Placebo**					**Paroxetine IR to Placebo**			
	Mean		95% CI			Mean		95% CI	
Change from Baseline at Week 12 LOCF Endpoint	3.8		-3.22, 10.73			5.4		-1.53, 12.35	
Baseline and Change in Baseline Q-LES-Q Social Relationships Scores									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	48.1	1.52	92	45.5	1.77	92	49.8	2.00	95
Change from Baseline at Week 12 LOCF Endpoint	18.9	2.14	92	21.3	2.14	92	9.0	2.10	95
Comparison	**Paroxetine CR to Placebo**					**Paroxetine IR to Placebo**			
	Mean		95% CI			Mean		95% CI	
Change from Baseline at Week 12 LOCF Endpoint	9.9		3.99, 15.76			12.3		6.46, 18.20	
Baseline and Change in Baseline Q-LES-Q General Activities Scores									
	Paroxetine CR			**Paroxetine IR**			**PBO**		
	Mean	SE	N	Mean	SE	N	Mean	SE	N
Baseline	46.1	1.31	92	44.5	1.45	91	45.5	1.58	95
Change from Baseline at Week 12 LOCF Endpoint	17.8	2.13	92	17.8	2.14	91	12.4	2.09	95
Comparison	**Paroxetine CR to Placebo**					**Paroxetine IR to Placebo**			
	Mean		95% CI			Mean		95% CI	
Change from Baseline at Week 12 LOCF Endpoint	5.4		-0.41, 11.29			5.4		-0.46, 11.25	
Q-LES-Q Overall Life Satisfaction Scores									
Baseline	**Paroxetine CR N=104**			**Paroxetine IR N=105**			**PBO N=101**		
Very Poor, n (%)	7 (6.7)			11 (10.5)			11 (10.9)		
Poor, n (%)	37 (35.6)			48 (45.7)			31 (30.7)		
Fair, n (%)	52 (50.0)			39 (37.1)			48 (47.5)		
Good, n (%)	8 (7.7)			7 (6.7)			10 (9.9)		
Very Good, n (%)	0 (0.0)			0 (0.0)			1 (1.0)		
Week 12 LOCF End Point	**Paroxetine CR N=92**			**Paroxetine IR N=92**			**PBO N=95**		

Very Poor, n (%)	4 (4.3)		7 (7.6)	10 (10.5)
Poor, n (%)	12 (13.0)		14 (15.2)	19 (20.0)
Fair, n (%)	25 (27.2)		21 (22.8)	21 (22.1)
Good, n (%)	36 (39.1)		32 (34.8)	38 (40.0)
Very Good, n (%)	15 (16.3)		18 (19.6)	7 (7.4)
Comparison	**Paroxetine CR to Placebo**		**Paroxetine IR to Placebo**	
	Mean Midrank Diff	95% CI	Mean Midrank Diff	95% CI
Week 12 LOCF Endpoint	-22.9	-50.66, 4.87	-20.2	-47.98, 7.55
Q-LES-Q Satisfaction with Medication Scores				
Baseline	**Paroxetine CR N=100**		**Paroxetine IR N=104**	**PBO N=98**
Very Poor, n (%)	8 (8.0)		10 (9.6)	10 (10.2)
Poor, n (%)	17 (17.0)		18 (17.3)	16 (16.3)
Fair, n (%)	40 (40.0)		53 (51.0)	41 (41.8)
Good, n (%)	30 (30.0)		19 (18.3)	29 (29.6)
Very Good, n (%)	5 (5.0)		4 (3.8)	2 (2.0)
Week 12 LOCF End Point	**Paroxetine CR N=92**		**Paroxetine IR N=92**	**PBO N=95**
Very Poor, n (%)	5 (5.4)		10 (10.9)	18 (18.9)
Poor, n (%)	13 (14.1)		8 (8.7)	11 (11.6)
Fair, n (%)	12 (13.0)		31 (33.7)	20 (21.1)
Good, n (%)	44 (47.8)		22 (23.9)	32 (33.7)
Very Good, n (%)	18 (19.6)		21 (22.8)	14 (14.7)
Comparison	**Paroxetine CR to Placebo**		**Paroxetine IR to Placebo**	
	Mean Midrank Diff	95% CI	Mean Midrank Diff	95% CI
Week 12 LOCF Endpoint	-28.5	-56.45, -0.58	-12.6	-40.52, 15.35

Safety Results:
Adverse experiences were classified as emergent if they occurred for the first time on or after the first day of randomized medication or they became more severe compared to baseline. Adverse experiences that occurred between the first and last doses of study medication were included in the On-Therapy study interval.

Most Frequent Adverse Events – On-Therapy	**Paroxetine CR N=104**	**Paroxetine IR N=105**	**PBO N=101**
Subjects with any AE(s), n(%)	95 (91.3)	95 (90.5)	81 (80.2)
Abnormal Ejaculation* (% corrected for gender)	14 (33.3)	13 (34.2)	1 (2.9)
Nausea	27 (26.0)	30 (28.6)	12 (11.9)
Headache	26 (25.0)	25 (23.8)	16 (15.8)
Somnolence	23 (22.1)	21 (20.0)	6 (5.9)
Respiratory Disorder	20 (19.2)	21 (20.0)	22 (21.8)
Asthenia	18 (17.3)	10 (9.5)	14 (13.9)
Diarrhea	18 (17.3)	21 (20.0)	7 (6.9)
Dry Mouth	16 (15.4)	9 (8.6)	11 (10.9)
Constipation	13 (12.5)	8 (7.6)	3 (3.0)
Dizziness	10 (9.6)	17 (16.2)	3 (3.0)
Insomnia	15 (14.4)	17 (16.2)	8 (7.9)
Infection	8 (7.7)	12 (11.4)	4 (4.0)
Dyspepsia	4 (3.8)	9 (8.6)	10(9.9)
Nervousness	5 (4.8)	9 (8.6)	8 (7.9)
Myalgia	5 (4.8)	3 (2.9)	10 (9.9)

Serious Adverse Events n (%) [n considered by the investigator to be related to study medication]	**Paroxetine CR N=104**	**Paroxetine IR N=105**	**PBO N=101**
Subjects with any SAEs, n (%) - Includes both fatal and non-fatal events	2 (1.9)	6 (5.7)	4 (4.0)

	n (%) [related]	n (%) [related]	n (%) [related]
Convulsion	1 (0.96) [0]	0	0
Myocardial Infarction	1 (0.96) [0]	0	0
Emotional Lability*	0	3 (2.9) [1]	0
Hepatocellular Jaundice	0	1 (0.95) [1]	0
Manic Reaction	0	1 (0.95) [0]	0
Uterine Fibroids Enlarged	0	0	1 (1.0) [0]
Gall Bladder Disorder	0	0	1 (1.0) [0]
Dehydration	0	0	1 (1.0) [0]
Accidental Overdose	0	0	1 (1.0) [1]
Subjects with fatal SAEs, n (%)	0	1 (0.95)	0
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Myocarditis	0	1 (0.95) [0]	0
* includes suicide attempt [n=2] and suicide ideation [n=1]			

Conclusion:
See publication below.

Publications:

Golden, R.N.; Nemeroff, C.B.; Mcsorley, P.; Pits, CD; Dube, E.M. (2002), Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J. Clin Psychiatry* 2002 Jul;63(7):577-584

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Antidepressant efficacy of controlled release paroxetine hcl. Golden, R N, Nemeroff, C B, Pitts, C D, and Dube, E M 41st Annual Meeting of the American College of Neuropsychopharmacology 12/8/2002 San Juan; Puerto Rico

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