The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: MY-1045/BRL-029060/1 (PAR128)
Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Comparison of Paroxetine and Fluoxetine in the Treatment of Major Depressive Disorder
Rationale: Compared to other Selective Serotonin Reuptake Inhibitors (SSRIs) such as fluoxetine and sertraline, paroxetine is more selective for the inhibition of serotonin reuptake than other neurotransmitters such as dopamine or norepinephrine. Thus, there is the potential advantage of reduced stimulant activity. The purpose of this trial was to compare the safety and efficacy of paroxetine to fluoxetine and placebo in the treatment of major depressive disorder. Of particular interest was the degree of anxiogenic activity reported by the subject. Additionally, there was interest in determining whether any differences existed between the two agents in ameliorating anxiety symptoms that frequently accompany depressive illness.
Phase: IIIb
Study Period: May 1991 to October 1991
Study Design: Multicenter, randomized, double-blind, placebo-controlled study
Centres: 23 in the United States
Indication: Major depressive disorder
Treatment: Placebo was taken during the 1-week washout period, followed by randomization (2.5:2.5:1) to paroxetine (PAR; 20 mg/day), fluoxetine (FLU; 20 mg/day), or placebo (PBO) for 12 weeks. The dosage allowed for all treatment groups was flexible and determined by the subject's therapeutic response to study medication. Dosage elevations were permitted at no less than 7-day intervals following the first week of the study and were determined by the subject's therapeutic response. Therapeutic response was according to the investigator's clinical judgement. The maximum dose was 50 mg/day for paroxetine, and 80 mg/day for fluoxetine. Dosage decreases were allowed at anytime during the trial, if an adverse event (AE) occurred.
Objectives: The primary objective of this study was to compare the safety and efficacy of paroxetine to fluoxetine and placebo in the treatment of subjects with major depressive disorder. Specifically, the intent of this investigation was to evaluate four outcomes: Antidepressant response Time to clinical antidepressant response Amelioration of symptoms related to anxiety Safety profiles of the active agents, particularly anxiogenic activity.
Primary Outcome/Efficacy Variables: The mean change from baseline in the total Hamilton Scale of Depression (HAMD) score at endpoint (after a last observation carried forward methodology).
Secondary Outcome/Efficacy Variables: The secondary efficacy parameters for evaluating antidepressant effects were: Proportion of subjects who achieved a decrease of ≥ 50% from baseline in the total HAMD score at any time during the 12-week study Proportion of subjects who achieved a HAMD score of ≤10 at any time during the 12-week study The time to clinical response, defined as the number of days to meet the HAMD criteria above HAMD subscales The Raskin Depression Scale total score The Clinical Global Impressions (CGI; severity of illness and global improvement items) The Global Assessment of Functioning (GAF). Symptoms Checklist 90 (SCL-90) total score and subscales The efficacy parameters for anxiolytic activity were assessed by: Change from baseline in the Covi Anxiety Scale, The HAMD Anxiety/Somatization cluster (HAMD items 10-13, 15 and 17) The Symptom Checklist-90 anxiety cluster (SCL 90 items 2, 17, 23, 33, 39, 57, 72, 78, 80, and 86).
Statistical Methods: The Intent-to-Treat (ITT) analysis included all randomized subjects. All randomized subjects who had an on-therapy efficacy evaluation were included in the efficacy analysis; all randomized subjects were included in the safety analysis. The main analysis was based on the extender dataset which modified the observed data so that missing data for a given week were estimated by bringing forward (extending) the data from the previous week. If

Week 1 data were missing, no estimate was made. Change from baseline scores (change = score – baseline score) of efficacy scales was analyzed using parametric analysis of variance methodology. The General Linear Models procedure of the SAS system was used to perform the analyses. Hypothesis testing concerning the significance of overall treatment effects was declared significant if the two-sided p-value was less than 0.05. Pairwise treatment effects were made when the overall treatment effect was significant, and a pairwise test was declared significant if the two-sided p-value was less than 0.05.

Study Population: Male and female outpatients, ≥18 years, with a primary diagnosis meeting Diagnostic and Statistical Manual of Mental Disorder (3rd edition) – Revised criteria for Major Depressive Disorder (MDD, single episode or recurrent) with a total score of ≥18 on the first 17 items of the 21-item Hamilton Depression rating scale (HAMD-21). Total scores could not have decreased by ≥25% between the screen and baseline visits. Subjects were excluded if they had a primary psychiatric diagnosis other than MDD. Other key exclusion criteria were: serious suicidal or homicidal risk, substance abuse/dependence, prior electroconvulsive therapy (within 3 months of the study), serious concomitant medical conditions, and subjects with a history of hypersensitivity to fluoxetine or who had previously taken paroxetine.

Number of Subjects:	**PAR**	**FLU**	**PBO**
Planned, N	250	250	100
Randomised, N	357	351	140
Completed, n (%)	220 (62)	237 (68)	78 (56)
Total Number Subjects Withdrawn, N (%)	137 (38)	114 (32)	62 (44)
Withdrawn due to Adverse Events (AEs) n (%)	61 (17)	32 (9)	6 (4)
Withdrawn due to Lack of Efficacy n (%)	9 (3)	16 (5)	21 (15)
Withdrawn due to Lack of Efficacy and AEs n (%)	11 (3)	9 (3)	7 (5)
Withdrawn for other reasons n (%)	56 (16)	57 (16)	28 (20)
Demographics	**PAR**	**FLU**	**PBO**
N (ITT)	357	351	140
Females: Males	222:135	215:136	100:40
Mean Age, years (SD)	42.3 (12.6)	40.6 (11.6)	43.3 (12.2)
Caucasian, n (%)	315 (88.2)	314 (89.5)	127 (90.7)
Major Depression, Single Episode, n (%)	141 (39.5)	141 (40.2)	43 (30.7)
Major Depression, Recurrent Episode, n (%)	216 (60.5)	210 (59.8)	97 (69.3)

Primary Efficacy Results:

	PAR	**FLU**	**PBO**	**Overall Treatment Difference**
N (ITT Efficacy Population)	350	344	136	-----
Mean Baseline HAMD Total Score	25.6 (0.22)	25.6 (0.22)	25.7 (0.35)	
Mean Change from Baseline in HAMD Extender Data	-11.8(0.47)	-13.0 (0.47)	-9.1 (0.74)	p<0.001
Pairwise Comparisons	PAR-FLU	PAR-PBO	FLU-PBO	
P-value	>0.05 (NS)	≤0.05	≤0.05	

Secondary Outcome Variables:

	PAR	**FLU**	**PBO**
N (ITT Population)	350	344	136
≥ 50% reduction in HAMD	62%	71%	51%
Pairwise Comparisons	PAR-FLU	PAR-PBO	FLU-PBO
Difference in percentage, 95% Confidence Interval (CI)	-9, (-15, -1)	11, (1, 21)	20, (9, 29)
Time to Response (≥ 50% reduction) in days (s.e.)	44 (1.8)	44 (1.7)	53 (2.6)
Pairwise Comparisons	PAR-FLU	PAR-PBO	FLU-PBO
Difference in time (days), 95% Confidence Interval (CI)	0.9, (-3.8, 5.7)	-8.4, (-14.6, -2.2)	-9.3, (-15.4, -3.2)
HAMD ≥ 10	54%	61%	43%
Pairwise Comparisons	PAR-FLU	PAR-PBO	FLU-PBO
Difference in percentage, 95% Confidence Interval (CI)	-6, (-14, 1)	9, (2, 21)	44, (8, 28)
Time to Response in days (s.e.)	57 (2.1)	57 (2.0)	60 (2.6)
Pairwise Comparisons	PAR-FLU	PAR-PBO	FLU-PBO
Difference in time (days), 95% Confidence Interval (CI)	-0.1, (-5.8, 5.5)	-3.4, (-9.9, -3.1)	-3.3, (-9.6, -3.1)

HAMD Anxiety/Somatization Factor			
Mean Baseline Score (s.e.)	7.2 (0.10)	7.2 (0.10)	7.5 (0.16)
Mean Change from Baseline at Endpoint (s.e.)	-3.0 (0.16)	-3.3 (0.16)	-2.5 (0.25)
HAMD Cognitive Disturbances Factor			
Mean Baseline Score (s.e.)	5.5 (0.12)	5.5 (0.12)	5.5 (0.19)
Mean Change from Baseline at Endpoint (s.e.)	-2.9 (0.15)	-3.1 (0.16)	-1.9 (0.24)
HAMD Retardation Factor			
Mean Baseline Score (s.e.)	8.1 (0.08)	8.1 (0.08)	7.9 (0.13)
Mean Change from Baseline at Endpoint (s.e.)	-3.9 (0.18)	-4.6 (0.18)	-3.1 (0.28)
HAMD Sleep Disturbance Factor			
Mean Baseline Score (s.e.)	3.4 (0.09)	3.4 (0.09)	3.7 (0.15)
Mean Change from Baseline at Endpoint (s.e.)	-1.4 (0.11)	-1.6 (0.11)	-1.3 (0.17)
HAMD Depressed Mood Factor			
Mean Baseline Score (s.e.)	2.8 (0.03)	2.8 (0.03)	2.7 (0.05)
Mean Change from Baseline at Endpoint (s.e.)	-1.5 (0.06)	-1.7 (0.07)	-1.1 (0.10)
HAMD Suicidality Factor			
Mean Baseline Score (s.e.)	1.1 (0.05)	1.1 (0.05)	1.2 (0.08)
Mean Change from Baseline at Endpoint (s.e.)	-0.7 (0.06)	-0.7 (0.06)	-0.5 (0.09)
HAMD Agitation Factor			
Mean Baseline Score (s.e.)	1.2 (0.05)	1.1 (0.05)	1.0 (0.08)
Mean Change from Baseline at Endpoint (s.e.)	-0.6 (0.05)	-0.6 (0.05)	-0.4 (0.08)
Raskin Total Score			
Mean Baseline Score (s.e.)	10.1 (0.08)	10.2 (0.08)	10.3 (0.13)
Mean Change from Baseline at Endpoint (s.e.)	-3.7 (0.16)	-4.1 (0.16)	-2.7 (0.25)
CGI Severity of Illness			
Mean Baseline Score (s.e.)	4.3 (0.03)	4.2 (0.03)	4.3 (0.05)
Mean Change from Baseline at Endpoint (s.e.)	-1.5 (0.07)	-1.7 (0.07)	-1.0 (0.12)
CGI Global Improvement, n (%)			
Very Much Improved, n (%)	132 (39.0%)	156 (44.4%)	35 (25.0%)
Much Improved, n (%)	74 (20.7%)	76 (21.7%)	25 (17.9%)
Minimally Improved, n (%)	61 (17.1%)	51 (14.5%)	32 (22.9%)
No Change, n (%)	58 (16.2%)	38 (10.8%)	29 (20.7%)
Minimally Worse, n (%)	18 (5.0%)	17 (4.8%)	10 (7.1%)
Much Worse, n (%)	5 (1.4%)	5 (1.4%)	4 (2.9%)
Very Much Worse, n (%)	1 (0.3%)	1 (0.3%)	1 (0.7%)
GAF			
Mean Baseline Score (s.e.)	56.1 (0.34)	55.8 (0.34)	56.1 (0.55)
Mean Change from Baseline at Endpoint (s.e.)	14.5 (0.76)	16.3 (0.75)	10.8 (1.14)
Total SCL-90			
Mean Baseline Score (s.e.)	105.7 (3.04)	108.9 (3.11)	111.9 (4.92)
Mean Change from Baseline at Endpoint (s.e.)	-43.8	-52.7	-32.1
SCL-90 Somatization Factor			

Mean Baseline Score (s.e.)	9.8 (0.44)	9.8 (0.46)	11.1 (0.72)
Mean Change from Baseline at Endpoint (s.e.)	-5.2 (0.52)	-6.7 (0.52)	-3.7 (0.81)
SCL-90 Interpersonal Sensitivity Factor			
Mean Baseline Score (s.e.)	12.3 (0.43)	12.3 (0.44)	12.3 (0.70)
Mean Change from Baseline at Endpoint (s.e.)	-6.0 (0.36)	-6.9 (0.36)	-3.8 (0.56)
SCL-90 Depression Factor			
Mean Baseline Score (s.e.)	23.8 (0.61)	24.7 (0.62)	24.7 (0.98)
Mean Change from Baseline at Endpoint (s.e.)	-10.2 (0.71)	-12.6 (0.71)	-7.0 (1.13)
SCL-90 Anxiety Factor			
Mean Baseline Score (s.e.)	10.7 (0.42)	10.9 (0.42)	11.0 (0.68)
Mean Change from Baseline at Endpoint (s.e.)	-4.0 (0.41)	-4.9 (0.41)	-2.8 (0.64)
SCL-90 Phobic Anxiety Factor			
Mean Baseline Score (s.e.)	3.5 (0.26)	3.2 (0.26)	3.5 (0.42)
Mean Change from Baseline at Endpoint (s.e.)	-1.6 (0.23)	-1.6 (0.24)	-1.4 (0.37)
SCL-90 Hostility Factor			
Mean Baseline Score (s.e.)	6.0 (0.29)	6.4 (0.29)	6.2 (0.47)
Mean Change from Baseline at Endpoint (s.e.)	-3.1 (0.26)	-3.6 (0.27)	-1.6 (0.42)
SCL-90 Obsessive/Compulsive Factor			
Mean Baseline Score (s.e.)	15.3 (0.47)	15.7 (0.49)	15.6 (0.77)
Mean Change from Baseline at Endpoint (s.e.)	-6.3 (0.46)	-7.5 (0.47)	-3.8 (0.72)
SCL-90 Paranoid Ideation Factor			
Mean Baseline Score (s.e.)	6.1 (0.29)	6.6 (0.29)	6.7 (0.47)
Mean Change from Baseline at Endpoint (s.e.)	-2.6 (0.24)	-3.3 (0.25)	-1.4 (0.38)
SCL-90 Psychotism Factor			
Mean Baseline Score (s.e.)	7.8 (0.35)	8.5 (0.36)	9.6 (0.57)
Mean Change from Baseline at Endpoint (s.e.)	-3.9 (0.25)	-4.5 (0.26)	-2.4 (0.41)
Covi Total Score			
Mean Baseline Score (s.e.)	6.4 (0.09)	6.5 (0.09)	6.6 (0.14)
Mean Change from Baseline at Endpoint (s.e.)	-1.2 (0.12)	-1.4 (0.12)	-1.2 (0.18)
HAMD Anxiety	-2.9	-3.3	-2.5
SCL-90 Anxiety	-4.0	-4.9	-2.8

Safety Results:

Most Frequent Adverse Events – On-Therapy	**PAR**	**FLU**	**PBO**
N (Safety Population)	357	351	140
Subjects with any AE(s), n (%)	330 (92.4)	323 (92.0)	117 (83.6)
Abnormal Ejaculation (% corrected for gender)	36 (26.7)	12 (8.8)	1 (2.5)
Asthenia	47 (13.2)	43 (12.3)	13 (9.3)
Constipation	41 (11.5)	21 (6.0)	12 (8.6)
Dyspepsia	31 (8.9)	40 (11.4)	9 (6.4)
Diarrhea	49 (13.7)	63 (18.0)	16 (11.4)
Dizziness	51 (14.3)	35 (10.0)	15 (10.7)
Dry Mouth	60 (16.8)	27 (7.7)	10 (7.1)
Headache	137 (38.4)	130 (37.0)	43 (30.7)
Insomnia	73 (20.5)	76 (21.7)	23 (16.4)

Nausea	107 (30.0)	81 (23.1)	22 (15.7)
Nervousness	60 (16.8)	65 (18.5)	11 (7.9)
Somnolence	84 (23.5)	58 (16.5)	10 (7.1)
Sweating	37 (10.4)	39 (11.1)	6 (4.3)
Tremor	42 (11.8)	49 (14.0)	4 (2.9)
Respiratory Disorder	28 (7.8)	30 (8.6)	12 (8.6)
Abdominal Pain	14 (3.9)	22 (6.3)	10 (7.1)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	**PAR n (%) [related]**	**FLU n (%) [related]**	**PBO n (%) [related]**
N (Safety Population)	357	351	140
Subjects with non-fatal SAEs, n (%)	9 (2.5)	7 (2.0)	4 (2.9)
Depression (worsening)	2(0.6) [0]	1 (0.3) [0]	2 (1.4) [1]
Emotional lability†	2 (0.6) [0]	2 (0.6) [0]	0
Neoplasm	1 (0.3) [0]	1 (0.3) [0]	0
Insomnia	1 (0.3) [1]	0	0
Nervousness	1(0.3) [1]	0	0
Carcinoma	1 (0.3) [0]	0	0
Epistaxis	1 (0.3) [1]	0	0
Gastrointestinal disorder	1 (0.3) [0]	0	0
Prostate disorder	1 (0.3) [0]	0	0
Coronary artery disorder	0	1 (0.3) [0]	0
Deep thrombophlebitis	0	1 (0.3) [0]	0
Hypoglycemia	0	1 (0.3) [0]	0
Rectal disorder	0	0	1 (0.7) [0]
Flu syndrome	0	0	1 (0.7) [0]
† Term may include: Completed suicides, self harm, suicidal thoughts, attempted suicide, crying and mood fluctuations.			

Conclusion:

Overall, the results of this study support the hypothesis that paroxetine and fluoxetine can be safely and effectively used to treat subjects with moderate or moderately severe depression.

Publications:

No publication

Date Updated: 04-Apr-2005