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-1043/BRL-029060/115

Title: A multicenter, randomized, double-blind, placebo-controlled comparison of paroxetine and fluoxetine in the treatment of major depressive disorder.

Rationale: . This study was designed to compare the clinical profiles of paroxetine (PAR) and fluoxetine (FLU) with specific emphasis on describing the time to clinical response and safety. 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: March 6, 1991 to October 31, 1991

Study Design: 12-Week, Randomized, double-blind, comparative, placebo-controlled.

Centres: 29 in USA

Indication: Major Depressive Disorder

Treatment: Following a one-week washout period with placebo (PBO), subjects were randomized (2.5:2.5:1) to either PAR (20 mg/day), FLU (20 mg/day), or PBO for 12 weeks. The dosage schedule was flexible and was determined by each patient's therapeutic response. Increases in dosage were permitted every three weeks beginning at week three. If response was inadequate using the Clinical Global Impression (CGI) of Severity of illness scale (score ≥2) then the dose was increased. For PAR patients the increase was in 10 mg increments to a maximum dose of 50 mg/day and for FLU the increase was in 20 mg increments to a maximum dose of 80 mg/day.

Objectives: To compare the safety and efficacy of PAR with PBO and FLU in the treatment of patients with major depressive disorder.

Primary Outcome/Efficacy Variable: . Hamilton Depression Scale (HAMD): proportion of patients who achieved a decrease of ≥50% in the total HAMD score at any time during the study; the proportion of patients who achieved a total HAMD score of ≤ 10; the time to clinical response, defined as the number of days until either a decrease of ≥50% in the total HAMD score or a total HAMD score of ≤ 10; mean change in baseline in the total HAMD score; the Raskin and CGI Severity of Illness and Global Improvement; anxiolytic activity determined by the Covi anxiety scale, HAMD anxiety/somatization cluster and the Symptom Check List 90 (SCL90) anxiety cluster. Changes in symptomology related to depression determined by analysing various factors of the HAMD and SCL90 scale and the Global Assessment of Functioning Scale (GAF).

Secondary Outcome/Efficacy Variable(s): Not applicable.

Statistical Methods: Analyses were performed on the Intent-to-Treat (ITT) population, which included all subjects who were randomised to study medication. For the safety analysis, this included the total patient population. The efficacy ITT population (depression, anxiety) only included all randomised patients with at least one on-therapy efficacy evaluation. Two types of datasets were used in the analyses: the visit-wise dataset consisted of the data for each subject at each visit; the extender dataset was generated from the visit-wise dataset; missing data were estimated by extending forward any post-baseline data from the previous visit. The results of greatest importance were those of the ITT population, extender dataset. The comparisons of treatment effects for proportion of patients with treatment response were analyzed using log-linear methods, with maximum likelihood parameter estimates. Changes from baseline scores were analyzed using parametric analysis of variance methodology. Time-to-event data were analyzed by product limit methods. The Wilcoxon Rank test was employed to determine whether differences in observed survival distributions were statistically significant. For all analyses pairwise comparisons were made only when the overall treatment effect was significant (p-value < 0.05).

Study Population: Outpatients ≥18 years old with moderate to moderately severe depression (DSM; single episode or recurrent). At both the screen visit and baseline the HAMD had to be at least 18 for the first 17 items; the HAMD total (21 items) could not decrease by more than 25% between screen and baseline visit. The Raskin depression score had to be at least 8 at baseline and must have exceeded the Covi Anxiety Score. Key exclusion criteria were patients with a primary psychiatric diagnosis other than depression, or those with serious concomitant diseases. Patients were excluded who had a serious suicidal threat, recent electroshock therapy, or with substance abuse.

	PAR	**FLU**	**PBO**
Number of Subjects:			
Planned, N	250	250	100
Randomised, N	284	289	118
Completed, n (%)	175 (61.6)	181 (62.6)	74 (62.7)

Total Number of Subjects Withdrawn, n (%)	109 (38.4)	108 (37.4)	44 (37.3)
Withdrawn due to Adverse Events, n (%)	39 (13.7)	29 (10.0)	8 (6.8)
Withdrawn due to Lack of Efficacy (LoE), n (%)	11 (3.9)	6 (2.1)	13 (11.0)
Withdrawn due to Adverse Events and LoE, n (%)	14 (4.9%)	10 (3.5%)	10 (8.5%)
Withdrawn for other reasons, n (%)	45 (15.8)	62 (21.5)	21 (17.8)
Demographics	**PAR**	**FLU**	**PBO**
N (ITT)	284	289	118
Females: Males	183 : 101	188 : 101	85 : 33
Mean Age, years (SD)	42.3 (12.5)	41.7 (11.3)	42.1 (11.6)
Caucasian, n (%)	253 (89.1)	253 (87.5)	109 (92.4)
Efficacy Results:			
HAMD – ITT population with at least one on-therapy efficacy evaluation, extender data set			
	PAR	**FLU**	**PBO**
N	272	278	113
Proportion of responders at any time: decrease ≥50%, n (%)	152 (56)	167 (60)	60 (53)
P-value for Overall Treatment Difference	0.355		
Treatment differences			
PAR minus FLU (95% CI)	-4 (-12, 4)		
PAR minus PBO (95% CI)	3 (-8, 14)		
FLU minus PBO (95% CI)	7 (-4, 18)		
Time to response (SE), days	54.2 (2.1)	53.2 (2.2)	53.0 (3.2)
p-value – treatment effect	0.583		
PAR vs FLU (95% CI)	1.0 (-5.0, 7.0)		
PAR vs PBO (95% CI)	1.2 (-6.2, 8.9)		
FLU vs PBO (95% CI)	0.2 (-7.3, 7.8)		
Proportion of responders at any time: score of ≤ 10; n (%)	131 (48)	139 (50)	52 (46)
P-value for Overall Treatment Difference	0.721		
Treatment differences			
PAR minus FLU (95% CI)	-2 (-10, 7)		
PAR minus PBO (95% CI)	2 (-9, 13)		
FLU minus PBO (95% CI)	4 (-7, 15)		
Time to response (SE), days	62.8 (2.1)	62.1 (2.2)	56.3 (3.0)
p-value – treatment effect	0.369		
PAR vs FLU (95% CI)	0.7 (-5.2, 6.6)		
PAR vs PBO (95% CI)	6.5 (-0.8, 13.6)		
FLU vs PBO (95% CI)	5.8 (-1.6, 13.1)		
	180	185	77
Change in Total score at endpoint (SE)	-10.6 (0.50)	-11.0 (0.49)	-9.1 (0.77)
p-value – treatment effect	0.108		
HAMD Analysis Mean changes from baseline: Factor & Item Analysis – ITT Extender data set			
	PAR	**FLU**	**PBO**
n	272	278	113
Total score (SE)	-10.6 (0.52)	-11.0 (0.52)	-9.1 (0.78)
Anxiety/Somatization (SE)	-2.9 (0.17)	-2.9 (0.17)	-2.7 (0.25)
Cognitive disturbance (SE)	-2.5 (0.15)	-2.7 (0.15)	-1.9 (0.23)
Retardation (SE)	-3.4 (0.19)	-3.7 (0.19)	-2.9 (0.29)
Sleep disturbance (SE)	-1.2 (0.13)	-1.2 (0.13)	-1.3 (0.20)
Depressed mood item (SE)	-1.4 (0.08)	-1.4 (0.08)	-1.1 (0.12)
Suicidality item (SE)	-0.7 (0.06)	-0.7 (0.06)	-0.5 (0.09)
Agitation item (SE)	-0.5 (0.06)	-0.5 (0.06)	-0.5 (0.09)
Raskin Depression Scale, Clinical Global Impressions & Global Assessment of Functioning Mean changes from baseline - ITT Extender data set			
	PAR	**FLU**	**PBO**

n	272	278	113
Change from Baseline in Raskin Total Score (SE)	-3.3 (0.18)	-3.3 (0.18)	-2.7 (0.27)
Change from Baseline in CGI – Severity of illness (SE)	-1.3 (0.12)	-1.3 (0.08)	-1.1 (0.11)
CGI – Global improvement (mean score at endpoint) (SE)	2.5 (0.08)	2.4 (0.08)	2.7 (0.12)
Change from Baseline in Global assessment of functioning (SE)	13.55 (0.80)	13.71 (0.79)	12.21 (1.19)

Clinical Global Improvement Scores - ITT Extender data set

	PAR	**FLU**	**PBO**
n	272	278	113
Very much improved n (%)	71 (26.1)	86 (30.9)	24 (21.2)
Much improved n (%)	69 (25.4)	73 (26.3)	24 (21.2)
Minimally improved n (%)	66 (24.3)	61 (21.9)	35 (31.0)
No change n (%)	43 (15.8)	35 (12.6)	26 (23.0)
Minimally worse n (%)	19 (6.9)	23 (8.3)	4 (3.5)
Much worse n (%)	4 (1.5)	0	0
Very Much Worse	0	0	0

Symptom Checklist (SCL-90) Mean changes from baseline - ITT Extender data set

	PAR	**FLU**	**PBO**
n	267	275	112
SCL-90 Total score (SE)	-44.6 (3.4)	-47.0 (3.3)	-30.2 (5.0)
Somatization (SE)	-4.2 (0.6)	-5.7 (0.6)	-4.7 (0.9)
Interpersonal sensitivity (SE)	-5.7 (0.4)	-6.2 (0.4)	-3.8 (0.6)
Depression (SE)	-10.3 (0.5)	-10.8 (0.8)	-7.5 (1.1)
Anxiety factor (SE)	-4.6 (0.5)	-4.6 (0.5)	-2.8 (0.7)
Phobic anxiety (SE)	-1.6 (0.3)	-1.7 (0.3)	-0.9 (0.4)
Hostility (SE)	-3.3 (0.3)	-3.6 (0.3)	-2.4 (0.4)
Obsessive/compulsive (SE)	-6.2 (0.5)	-6.2 (0.5)	-4.4 (0.8)
Paranoid ideation (SE)	-2.9 (0.3)	-3.0 (0.3)	-2.0 (0.4)
Psychoticism (SE)	-3.5 (0.4)	-3.9 (0.4)	-2.4 (0.6)

Covi Scale and SCL-90 Anxiety Cluster Mean changes from baseline score - ITT Extender data set

	PAR	**FLU**	**PBO**
n	272	278	113
Covi Total score n, mean (SE)	272, -1.3 (0.1)	278, -1.4 (0.1)	113, -1.2 (0.2)
SCL-90 anxiety factor n, mean (SE)	267, -4.6 (0.5)	275, -4.6 (0.5)	112, -2.8 (0.7)

Anxiolytic Activity Summary for High and Low (Covi score ≥ 7 & <7) Mean changes from baseline - ITT

Anxiety Variables	**Baseline Anxiety Level**	**PAR**		**FLU**		**PBO**	
		n	**Mean**	**n**	**Mean**	**n**	**Mean**
HAMD anxiety/somatization	Low	138	-2.5	152	-2.7	71	-2.8
	High	134	-3.1	126	-3.1	42	-1.9
95% CI PAR and FLU	Low	-0.55, 0.77					
	High	-0.74, 0.66					
SCL-90 Anxiety factor n, mean	Low	136	-3.2	151	-3.3	71	-2.5
	High	131	-5.8	124	-6.1	40	-3.3
95% CI PAR and FLU	Low	-1.49, 1.79					
	High	-1.53, 1.95					

Antidepressant Activity Summary for High and Low (Covi score ≥ 7 & <7) Mean changes from baseline - ITT

Depression Variables	**Baseline Anxiety Level**	**PAR**		**FLU**		**PBO**	
		n	**Mean**	**n**	**Mean**	**n**	**Mean**
HAMD Total	Low	138	-9.5	152	-10.5	71	-10.0
	High	134	-11.1	126	-11.5	42	-7.5
95% CI PAR and FLU	Low	-0.93, 2.85					
	High	-1.60, 2.40					

CGI Severity of Illness	Low	138	-1.1	152	-1.2	71	-1.1
	High	134	-1.3	126	-1.3	42	-0.9
95% CI PAR and FLU	Low	-0.24, 0.03					
	High	-0.35, 0.25					

Safety Results:
Safety evaluations were conducted by monitoring of AEs, vital signs, clinical laboratory parameters and the Abnormal Involuntary Movement Scale (AIMS). AEs reported are only those occurring during the study treatment period (post-baseline).

	PAR	**FLU**	**PBO**
Most Frequent Adverse Events on Therapy –			
Subjects with any AE(s), n(%)	264 (93)	255 (88)	103 (87)
Headache	104 (37)	105 (36)	50 (42)
Nausea	76 (27)	70 (24)	14 (12)
Somnolence	69 (24)	51 (18)	9 (8)
Insomnia	57 (20)	60 (21)	18 (15)
Asthenia	49 (17)	33 (11)	10 (8)
Dizziness	47 (17)	30 (10)	10 (8)
Nervousness	47 (17)	39 (13)	14 (12)
Diarrhoea	45 (16)	42 (15)	9 (8)
Dry mouth	43 (15)	29 (10)	4 (3)
Tremor	34 (12)	31 (11)	3 (3)
Dyspepsia	30 (11)	37 (13)	12 (10)
Flatulence	24 (8)	15 (5)	10 (8)
Respiratory disorder	19 (7)	23 (8)	11 (9)
Trauma	15 (5)	15 (5)	11 (9)
Back pain	11 (4)	19 (7)	12 (10)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to the study medication]			
	PAR	**FLU**	**PBO**
Subjects with non-fatal SAEs, n (%)	11 (4)	8 (3)	6 (5)
Hypertension	1 (0.4)[n/a]	0	0
Diabetes and hypothyroidism	1 (0.4) [n/a]	0	0
Fibrocystic disease (mastectomy)	1 (0.4) [n/a]	0	0
Ovarian cysts (hysterectomy)	1 (0.4) [n/a]	0	0
Peptic ulcer hemorrhage	1 (0.4) [n/a]	0	0
Spinal surgery*	1 (0.4) [n/a]	0	0
Hypomanic episode w/ suicidal tendency	1 (0.4) [n/a]	0	0
Suicidal ideation/thought/gesture	2 (0.7) [n/a]	1 (0.3) [n/a]	1 (0.8)** [n/a]
Alcoholism	1 (0.4) [n/a]	0	0
Neoplasm	1 (0.4) [n/a]	1 (0.3) [n/a]	0
Acute pyelonephritis	0	2 (0.7) [n/a]	0
Thrombophlebitis	0	1 (0.3) [n/a]	0
Ectopic pregnancy	0	1 (0.3) [n/a]	0
Polycystic granuloma	0	1 (0.3) [n/a]	0
Basal cell carcinomas	0	2 (0.7) [n/a]	0
Back pain	0	0	1 (0.8) [n/a]
Trauma	0	0	1 (0.8) [n/a]
Viral meningitis	0	0	1 (0.8) [n/a]
Infection	0	0	1 (0.8)** [n/a]
Myocardial infarction	0	0	1 (0.8) [n/a]
Mole removal	0	0	1 (0.8) [n/a]
Subjects with fatal SAEs, n (%)	0	1 (0.3) [n/a]	0
Myxoid mitral valve		1 (0.3) [n/a]	
*4 days after trial completion; ** same patient;			

Conclusion: The magnitude of change from baseline in the HAMD rating scores for paroxetine- and fluoxetine-treated subjects was similar, and, both exhibited greater change than placebo-treated subjects although statistical significance was not achieved.
Publications: No publication

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