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- 1028/BRL-029060/1/CPMS-118
Title: Paroxetine versus Clomipramine and Placebo in the Treatment of Obsessive-Compulsive Disorder
Rationale: The antidepressant paroxetine is a phenylpiperidine compound that acts via potent and selective inhibition of serotonin reuptake. The effectiveness of paroxetine as an antidepressant has been demonstrated in outpatients with major depressive disorders, inpatients with severe depression and depressed patients with associated symptoms of anxiety. Fewer and less troublesome anticholinergic side effects occur with paroxetine than with the tricyclic antidepressants, and few reports of serious illness have been associated with paroxetine treatment. This trial was designed to assess the effectiveness of paroxetine versus placebo in the treatment of OCD, and compare its safety, tolerability profile versus placebo and clomiprarnine
Phase: III
Study Period: August 1991 to November 1993
Study Design: Multi-center, 12 week, randomized, double-blind, parallel group study
Centres: 13 in USA
Indication: Obsessive-compulsive disorder (OCD)
Treatment: A two-week, single-blind placebo pretreatment phase was used to screen potential candidates for inclusion in the study. Eligible subjects were randomized (1:1:1) to one of three treatment groups: paroxetine in daily doses starting at 20 mg, clomipramine in daily doses starting at 25 mg, or placebo. Depending on the therapeutic response, the paroxetine daily dose was increased in increments of 10 mg to a maximum of 60 mg, and the clomipramine daily dose was increased in increments of 25 mg to a maximum of 250 mg. Dose changes could be made no more frequently than every fourth day. The maximum length of double-blind medication treatment was 12 weeks. Subjects had the opportunity to continue onto the long-term extension study, 127.
Objectives: To demonstrate the effectiveness and safety of paroxetine in the treatment of OCD in a 12-week, randomized, double-blind, placebo- and clomipramine-controlled study.
Primary Outcome/Efficacy Variable: Yale-Brown Obsessive-Compulsive Scale (YBOCS) total score, evaluations included the mean change from baseline for all visits at which this variable was assessed and from baseline to endpoint. Baseline mean scores were also compared across the three treatment groups.
Secondary Outcome/Efficacy Variable(s): YBOCS Obsessive and Compulsive subtotal scores, National Institute of Mental Health Obsessive-Compulsive Scale (NIMHOCS) scores, items of Clinician Global Impression (CGI), and Symptom Checklist-90 (SCL-90), Hamilton Depression Rating Scale (HAMD), and Global Assessment Functioning (GAF) scales. Evaluations included the mean change from baseline for all visits at which these variables were assessed and from baseline to endpoint, except for CGI Global Improvement and Efficacy Index. The percentage of subjects responding was analyzed by the proportion achieving at least a 25% reduction from baseline in the YBOCS total score, subjects achieving a decrease of two or more points from the baseline CGI Severity of Illness score, and subjects achieving a CGI Improvement Score of one or two.
Statistical Methods: The Intent-to-Treat (ITT) population used for the safety analysis consisted of all subjects randomized to study medication. The primary efficacy analysis used the ITT population but only included randomized subjects with at least one on-therapy efficacy evaluation. For inclusion in the analysis there was no time limit between the day of a subject's last dose and the day of a subsequent efficacy evaluation. The primary analyses used the extender (Last Observation Carried Forward) dataset at week 12. The extender dataset carries any data forward from the last visit for any missing data at a visit. Change from baseline scores of efficacy scales were analyzed using parametric ANOVA methodology. Some efficacy scales were not evaluated at baseline, so the raw scores of these scales were used. The General Linear Models (GLM) procedure of the SAS was used to perform the analyses. Proportions of subjects achieving a dichotomous response were analyzed using log-linear model methodology via the categorical model procedure of the SAS system (CATMOD). Weighted least squares parameter estimations were used. Tests of hypothesis concerning interaction terms were declared significant if the p-values were less than 0.10. Tests of hypotheses concerning the significance of overall treatment effects were declared significant if the p values were less than 0.05. Pairwise comparisons were made only when the overall treatment effect was significant ($p<0.05$). Pairwise comparisons were made using the CONTRAST statement. The pairwise comparison between paroxetine and placebo was the primary proof of efficacy in this study. Power calculation: There were to be 100 subjects enrolled in each treatment group. This sample size would provide at least 98% power at a two-tailed alpha level (0.05) to detect a 10 point difference with a standard deviation of 7.3 points in the change from baseline in the YBOCS Score for the paroxetine versus the placebo comparison.

Study Population: Outpatients who were ≥16 years old with a diagnosis of OCD Diagnostic and Statistical Manual of Mental Disorders 3rd edition (revised) (DSM-IIIR 300.30) were eligible for participation in the study. Trichotillomania could be present and there must have been a documented history of OCD of ≥6 months duration. Each subject must have met the DSM-IIIR diagnostic criteria for OCD, had a baseline score of 7 or above on the NIMHOCS and had a baseline score of 16 or above on the YBOCS. The subject must have had a HAMD score at both the screen and baseline visits of ≤16 on the first 17 items of the scale and the score on item 1 must not have exceeded 2. Subjects were excluded if they had: any principal Axis I disorders other than OCD or had a history of major depressive disorder within the last 3 months; personality disorders of sufficient severity to compromise their participation in the study; body dysmorphic disorder as a primary diagnosis (DSM-IIIR 300.70); a history of bipolar affective disorders; a history of seizure disorders, a requirement for concomitant therapy with other psychotropic drugs; had abused alcohol or drugs within the past 6 months; posed a serious suicidal or homicidal risk; received other psychotropic drugs within 14 days of the baseline visit; had previously received paroxetine; were pregnant, lactating or were of childbearing potential and did not use adequate contraception; were participating in ongoing behavioral therapy.

Number of Subjects:	**placebo**	**paroxetine**	**clomipramine**
Planned, N	100	100	100
Randomised, N	77	82	82
Completed, n (%)	57	54	54
Total Number Subjects Withdrawn, N (%)	20 (26.0)	28 (34.1)	28 (34.1)
Withdrawn due to Adverse Events n (%)	8 (10.4)	15 (18.3)	17 (20.7)
Withdrawn due to Lack of Efficacy n (%)	4 (5.2)	1 (1.2)	0 (0)
Withdrawn for other reasons n (%)	8 (10.4)	12 (14.6)	11 (13.4)
Demographics			
N (ITT)	77	82	82
Females: Males.	23:54	38:44	34:48
Mean Age, years (SD).	36.3 (10.7)	41.3 (11.7)	36.0 (11.4)
Caucasian n (%)	71 (92.2)	77 (93.9)	75 (91.5)

Primary Efficacy Results: (ITT extender dataset) [95% confidence interval not available]

	placebo	**paroxetine**	**clomipramine**	**p-value**
YBOCS total, mean (SE)	N=75	N=79	N=78	
Baseline	24.66 (0.55)	23.28 (0.53)	23.90 (0.54)	0.183
Change at Week 12 extender set	-4.61 (0.87)	-5.61(0.84)	-7.73 (0.84)	0.027

Secondary Outcome Variable(s):[95% confidence intervals not available]

	placebo n=75	**paroxetine n=79**	**clomipramine n=78**
YBOCS obsessive subtotal, mean (SE)			
Baseline	12.22 (0.33)	11.37 (0.32)	11.81 (0.32)
Change at Week 12 extender set	-2.33 (0.47)	-3.10 (0.46)	-3.83 (0.46)
YBOCS compulsive subtotal, mean (SE)			
Baseline	12.44 (0.33)	11.91 (0.32)	12.08 (0.32)
Change at Week 12 extender set	-2.29 (0.46)	-2.51 (0.45)	-3.90 (0.45)
NIMHOCS, mean (SE)			
Baseline	8.86 (0.14)	8.75 (0.14)	8.90 (0.14)
Change at Week 12 extender set	-1.04 (0.24)	-1.42 (0.23)	-2.06 (0.23)
CGI severity of illness, mean (SE)			
Baseline	4.61 (0.08)	4.54 (0.08)	4.50 (0.08)
Change at Week 12 extender set	-0.44 (0.11)	-0.62 (0.11)	-0.82 (0.11)
CGI global improvement, mean (SE)			
Week 1 extender set	3.79 (0.08)	3.90 (0.07)	3.72 (0.07)
Week 12 extender set	3.26 (0.13)	2.91 (0.12)	2.71 (0.12)
CGI efficacy index, mean (SE)			
Week 1 extender set	-0.04 (0.04)	-0.28 (0.04)	-0.27 (0.04)*
Week 12 extender set	0.16 (0.05)	0.02 (0.05)	-0.05 (0.05)

HAMD total	n=67	n=66	n=64
Baseline, mean (SE)	9.83 (0.52)	10.33 (0.51)	9.82 (0.53)
Week 12 extender set, mean (SE)	-0.42 (0.61)	-1.18 (0.61)	-2.18 (0.62)
GAF	n=74	n=75	n=71
Baseline	53.91 (0.97)	54.93 (0.95)	55.52 (0.98)
Change at Week 12 extender set	4.06 (1.27)	5.81 (1.24)	5.57 (1.28)
SCL-90	n=74	n=74	n=69
Baseline	77.44 (5.54)	77.89 (5.45)	80.53 (5.67)
Change at Week 12 extender set	-9.16 (4.62)	-19.68 (4.54)	-22.40 (4.73)
Number (%) of subjects responding to treatment by YBOC total score reduced by at least 25% from baseline			
Week 1 extender set (%)	5/73 (6.8)	5/73 (6.8)	6/74 (8.1)
Week 12 extender set (%)	32/75 (42.7)	35/79 (44.3)	40/78 (51.3)
Number (%) of subjects responding to treatment by at $\geq$2 point decrease from baseline in CGI severity of illness			
Week 1 extender set (%)	0/72	0/72	0/74
Week 12 extender set (%)	7/75 (9.3)	14/79 (17.7)	18/78 (23.1)
Number (%) of subjects responding to treatment by CGI global improvement of 1 or 2			
Week 1 extender set (%)	2/72 (2.8)	1/72 (1.4)	3/74 (4.1)
Week 12 extender set (%)	19/75 (25.3)	28/79 (35.4)	34/78 (43.6)

Safety Results:

Safety was assessed by adverse event reporting at each subject visit after screening either by direct observation, spontaneously reported by the subject or subject response to a non-leading question. An on-therapy adverse event (AE) or serious adverse event (SAE) was defined as an AE or SAE occurring during treatment or within 30 days of stopping treatment.

Most Frequent Adverse Events On-Therapy	**placebo**	**paroxetine**	**clomipramine**
Subjects with any AE(s), n(%)	67 (87.0)	77 (93.9)	80 (97.6)
Abnormal ejaculation *	1 (1.9)	13 (29.5)	11 (22.9)
Asthenia	10 (13.0)	12 (14.6)	22 (26.8)
Constipation	5 (6.5)	18 (22.0)	27 (32.9)
Depression	6 (7.8)	1 (1.2)	3 (3.7)
Dizziness	4 (5.2)	18 (22.0)	32 (39.0)
Dry mouth	9 (11.7)	17 (20.7)	48 (58.5)
Diarrhea	8 (10.4)	8 (9.8)	3 (3.7)
Headache	29 (37.7)	26 (31.7)	20 (24.4)
Insomnia	9 (11.7)	21 (25.6)	26 (31.7)
Nausea	6 (7.8)	26 (31.7)	19 (23.2)
Nervousness	9 (11.7)	7 (8.5)	14 (17.1)
Respiratory disorder	11 (14.3)	9 (11.0)	6 (7.3)
Rhinitis	6 (7.8)	0 (0)	2 (2.4)
Sinusitis	6 (7.8)	1 (1.2)	1 (1.2)
Somnolence	5 (6.5)	33 (40.2)	31 (37.8)
Sweating	0 (0)	7 (8.5)	24 (29.3)
Tremor	0 (0)	10 (12.2)	26 (31.7)
* % corrected by gender			
Serious Adverse Events -On therapy n (%) [considered by the investigator to be related to study medication]	**placebo**	**paroxetine**	**clomipramine**
Subjects with non-fatal SAEs, n (%)	4 (5.2) [0]	2 (2.4) [1]	0 (0)
Testicular/groin pain	0	1 [1]	0
Pulmonary embolus	0	1 [0]	0
Auto accident, head injury, unconscious	1 [0]	0	0
Exacerbation of OCD	1 [0]	0	0
Chest pains (during placebo pre-treatment phase)	1 [0]	0	0
Obsessive-compulsive behaviour increased	1 [0]	0	0

Subjects with fatal SAEs, n (%)	0	0	0
Conclusion Reductions from baseline in disease-specific psychometric measures in the paroxetine group were not statistically significant. The frequency of commonly reported adverse events in the paroxetine group tended to be similar to the clomipramine group.			
Publications: No publication			

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