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Study No.: MY-1053/BRL-029060/CPMS-127
Title: Long-term treatment with paroxetine of outpatients with obsessive-compulsive disorder: An extension of the companion study.
Rationale: Obsessive-Compulsive Disorder (OCD) is often chronic, disabling and refractory to conventional therapies. The essential features of this disorder are recurrent obsessions or compulsions, sufficiently severe to cause marked distress, be time-consuming or significantly interfere with the person's normal routine, occupational functioning, usual social activities or relationships with others. The present study evaluates the ability of long term paroxetine therapy in preventing relapse of OCT after response to acute treatment. This study is an extension to the flexible dose paroxetine study (PAR 118).
Phase: III
Study Period: 8 January 1992 to 8 November 1994
Study Design: Multicenter, 12 month extension study of outpatients with OCD. Patients who completed 12 weeks of the double phase of study 118 were permitted to be screened into this study. The first part of the study consisted of a 6 month open-label phase. At the end of the open-label phase, only those subjects with a therapeutic response were permitted to enter the double-blind phase. A therapeutic response was defined as a reduction in the total Y-BOCS score of 25% or more from the baseline value established at the inception of the 12-week, double blind, study 118, and a decrease of at least 2 points on the Severity of Illness item of the CGI. Those subjects who did not achieve a therapeutic response were withdrawn from the study. Those patients that were randomised entered a 6 month phase to assess full therapeutic relapse. Full therapeutic relapse was defined as a return to the Y-BOCS score to the baseline value or more established at the inception of the 12 week double-blind study 118 **and** an increase of 1 point or more on the CGI severity of illness scale established at the last acute observation of the open label phase of the study. Also partial relapse was defined as a measure of efficacy, partial relapse was defined as either of the two definitions for full relapse instead both of them.
Centres: 13 in USA
Indication: Obsessive-compulsive disorder (OCD)
Treatment: The study began with a 2-week taper (phase I) of the final dosage attained in study 118. The study was then divided into a 6-month open-label phase (phase II) with flexible PAR dosing (20-60 mg/day) followed by a 6-month randomised phase (phase III) in which patients were assigned (1:1) to PAR (same dose as at end of open-label phase) or placebo (PBO) to asses the prevention of relapse upon cessation of therapy. There was a 1-month, no treatment, follow-up phase for all patients who prematurely terminated from the study with an adverse experience or who completed the study with an ongoing adverse experience.
Objectives: To demonstrate the long-term clinical response to PAR and to assess its safety/tolerability in the treatment of outpatients with OCD; and to assess the prevention of relapse of OCD.
Primary Outcome/Efficacy Variable: Open label phase: Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score. Randomised phase: proportion of patients who relapse and time to partial relapse; Y-BOCS total score.
Secondary Outcome/Efficacy Variable(s): Open-label phase: Y-BOCS obsession subscale; Y-BOCS compulsion subscale; National Institute of Mental Health Obsessive-Compulsive Scale (NIMHOCS); Clinician Global Impression (CGI) severity of illness item; CGI global improvement item, CGI efficacy index; percent of patients responding to treatment. Randomisation phase: Y-BOCS obsession subscale; Y-BOCS compulsion; NIMHOCS; CGI severity of illness item; CGI global improvement item; CGI efficacy index.
Statistical Methods: Analyses were performed on the Intent-to-Treat (ITT) population. The safety ITT analysis included all subjects who were randomised to study medication. The efficacy ITT analysis for the open-label phase included any patient receiving open-label drug and having at least one efficacy assessment during the open-label phase. For the randomisation phase, efficacy analyses included any patients who completed the open-label phase, received coded medication and had at least one efficacy assessment during the randomisation phase; this was the primary population of interest. Time to clinical relapse and time to withdrawal during the randomisation phase were analysed using the Cox proportional hazards methodology. The proportion of patients relapsing was analysed using the Fisher's exact Test. Change from baseline of efficacy scales during the randomisation phase were analysed using parametric analysis of

variance methodology. Test of hypotheses concerning the differences between the treatment groups were declared significant at an alpha level of 0.05.
Power calculation: Based on the target sample size in study PAR-118 (100/group), up to 300 patients could be enrolled in PAR-127. Calculation of sample size was based only detecting statistically significant differences between the PAR and PBO groups in PAR-118. A total of 154 patients with a clinical diagnosis of OCD who completed the 12-week, short-term study, flexible dosing (PAR-118) were enrolled in the study.

Study Population :

To be eligible, patients had to meet the following inclusion criteria:

- Patients were required to have completed the 12-week randomised, double-blind, flexible dose PAR-118 study
- Patients had to meet DSM-IIIR diagnostic criteria for OCD and be ≥ 16 years old

Key exclusion criteria:

- Patients who withdrew prematurely from PAR-118
- Patients diagnosed with an Axis I disorder other than OCD; had a major depressive order during the previous 6 months; had a personality disorder which would compromise study participation; had a body dysmorphic disorder; a history of seizures; required concomitant psychotropic drugs (except chloral hydrate)
- Patients who posed a serious suicide or homicide risk.
- Women of childbearing potential (women were to be ≥6 months post menopausal to be classified as of non-childbearing potential)
- Patients participating in ongoing behavioral therapy

	Open-label phase	**Randomised phase PAR**	**Randomised phase PBO**
Number of Subjects:			
Planned, N	154	77	77
Randomised, N	144	20	24
Completed, n (%)	78	11	8
Withdrawn, n (%)	100	9	16
Demographics			
N (ITT)	144	20	24
Females: Males.	54:90	9:11	9:15
Mean Age, years (SD).	38.5 (11.7)	40.7 (10.5)	41.1 (12.5)
Caucasian n (%)	131 (91.0)	19 (95.0)	22 (91.7)

Primary Efficacy Results:

Open label phase	**n**	**PAR**
Baseline and change in Y-BOCS total, mean (SE)		
Baseline	140	24.23 (0.39)
Endpoint	140	-8.04 (0.66)
≥Month 6	81	-11.99 (0.86)

Randomised phase

Proportion of patients who relapsed	**PAR**	**PBO**	**p-value**
Full relapse n/total (%)	0/19 (0)	4/22 (18.2)	0.111
median, mean	0,0	30.0, (36.5)	
Partial relapse n/total (%)	8/19 (42.1)	14/22 (63.6)	0.217
median, mean	28.0, 43.5	26.5, 40.0	

Time to relapse	**PAR**	**PBO**	**p-value**	**risk ratio**	**95% CI**
Partial relapse (median)	43.5 days (28.0)	40 days (26.5)	0.159	1.9	0.8, 4.5
Full relapse *					

* due to the small number of patients who experienced a full relapse, survival analysis of the time to full relapse during the randomization phase was not done.

Baseline and change in Y-BOCS total, mean (SE)	**PAR** N		**PBO** n		**p-value**
Baseline	19	10.11 (1.34)	22	10.45 (1.25)	0.850
Month 12	12	-3.50 (1.04)	8	0.88 (1.27)	0.016

Secondary Outcome Variable(s):		
Open label phase		
Baseline and change in Y-BOCS obsessive subtotal, mean (SE)	**n**	**PAR**
Baseline (Study 118)	140	12.02 (0.23)
Endpoint (Study 118)	140	-4.20 (0.35)
≥Month 6	81	-6.43 (0.46)
Baseline and change in Y-BOCS compulsive subtotal, mean (SE)	**n**	**PAR**
Baseline (Study 118)	140	12.21 (0.22)
Endpoint (Study 118)	140	-3.84 (0.36)
≥Month 6	81	-5.56 (0.46)
Baseline and change in NIMHOCS score, mean (SE)	**n**	**PAR**
Baseline (Study 118)	140	8.68 (0.10)
Endpoint (Study 118)	140	-2.08 (0.19)
≥Month 6	81	-3.56 (0.27)
Baseline and change in CGI severity of illness, mean (SE	**n**	**PAR**
Baseline (Study 118)	140	4.49 (0.06)
Endpoint (Study 118)	140	-0.89 (0.09)
≥Month 6	81	-1.62 (0.12)
Baseline and change in CGI global improvement, mean (SE)	**n**	**PAR**
Endpoint (Study 118)	140	2.64 (0.09)
≥Month 6	81	2.02 (0.11)
Baseline and change in CGI efficacy index, mean (SE)	**n**	**PAR**
Endpoint (Study 118)	140	0.18 (0.03)
≥Month 6	80	0.04 (0.05)
Proportion of patients responding to treatment , n/total	**PAR**	
Endpoint (Study 118)	34/140 (24.3)	
≥Month 6	47/81 (58.0)	

Randomised phase				
Baseline and change in Y-BOCS obsessive subtotal, mean (SE)	**PAR** **n**		**PBO** **N**	
Baseline	19	4.79 (0.69)	22	4.55 (0.64)
Month 12	12	-2.33 (0.68)	8	0.25 (0.83)
Baseline and change in Y-BOCS compulsion subtotal, mean (SE)	**PAR** **n**		**PBO** **N**	
Baseline	19	5.32 (0.81)	22	5.91 (0.75)
Month 12	12	-1.17 (0.61)	8	0.63 (0.74)
Baseline and change in NIMHOCS score, mean (SE)	**PAR** **n**		**PBO** **N**	
Baseline	19	4.53 (0.46)	22	4.55 (0.43)
Month 12	12	-0.67 (0.48)	8	0.38 (0.59)
Baseline and change in CGI severity of illness, mean (SE)	**PAR** **n**		**PBO** **N**	
Baseline	19	2.63 (0.22)	22	2.68 (0.20)
Month 12	12	-0.08 (0.16)	8	-0.13 (0.20)
CGI severity of illness, mean (SE)	**PAR** **n**		**PBO** **N**	
Month 12	12	1.83 (0.18)	8	1.75 (0.22)
CGI efficacy index, mean (SE)*)*	**PAR** **n**		**PBO** **N**	
Month 12	12	0.65 (0.10)	8	0.70 (0.12)

Safety Results:
An on therapy adverse event (AE) was defined as an AE occurring during treatment or within 14 days of stopping treatment.

Most Frequent Adverse Events On-Therapy

Onset during Open label phase

	Paroxetine
Subjects with any AE(s), n (%)	137 (95.1)
Somnolence	44 (30.6)
Insomnia	37 (25.7)
Headache	36 (25.0)
Nausea	31 (21.5)
Dizziness	28 (19.4)
Asthenia	25 (17.4)
Constipation	18 (12.5)
Diarrhea	15 (10.4)
Dry Mouth	15 (10.4)
Weight gain	15 (10.4)
Respiratory disorder	15 (10.4)

Randomised phase

	PAR	**PBO**
Subjects with any AE(s), n (%)	13 (65.0)	19 (79.2)
Insomnia	4 (20.0)	2 (8.3)
Headache	3 (15.0)	7 (29.2)
Diarrhea	3 (15.0)	5 (20.8)
Sinusitis	3 (15.0)	4 (16.7)
Pain	2 (10.0)	0
Dizziness	2 (10.0)	9 (37.5)
Parasthesia	2 (10.0)	2 (8.3)
Somnolence	2 (10.0)	1 (4.2)
Cough Increased	2 (10.0)	0
Asthenia	1 (5.0)	3 (12.5)
Dyspepsia	1 (5.0)	3 (12.5)
Nausea	1 (5.0)	3 (12.5)
Respiratory disorder	1 (5.0)	3 (12.5)
Concentration impaired	1 (5.0)	2 (8.3)
Nervousness	0	3 (12.5)
Infection	0	2 (8.3)
Abnormal dreams	0	2 (8.3)
Agitation	0	2 (8.3)
Emotional Lability*	1 (5.0)	1 (4.2)
* Term may include the following events: Completed suicides, self harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations.		

Serious Adverse Events -On therapy n (%) [considered by the investigator to be related to study medication]

	PAR	**PBO**
Subjects with non-fatal SAEs, n (%)	2 (1.4)[0]	0
Alcoholism (hospitalised)	1 [0]	0
Infarct of lower bowel (hospitalised, relatedness unassessable)	1 [0]	0
Subjects with fatal SAEs, n (%)	0	0

Conclusion:
The effectiveness of paroxetine in the long-term treatment of patients with OCD is supported by maintained improvement of their OCD symptoms during the 6-month open-label phase. In the randomization phase, patients who were switched to PBO relapsed more quickly and in greater proportion than patients who maintained their paroxetine treatment, although these differences were not statistically significant. Long-term treatment with paroxetine resulted in

few new adverse events and no dramatic increases in the frequency of adverse events.
Publications: No publication.

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