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-1050/BRL-029060/1/CPMS-222 (PAR 222)
Title: A Double-Blind, Placebo-Controlled, Continuation of Study 29060/120 to Assess the Long Term Safety and Efficacy of Paroxetine in the Treatment of Panic Disorder and its Role in the Prevention of Relapse/Recurrence
Rationale: In a recent dose-ranging study (29060/120), the efficacy of paroxetine (PAR) treatment over 10 weeks at daily doses of 10, 20, and 40 mg was evaluated in a placebo-controlled, double-blind fashion in outpatients with panic disorder. This was a 6-month continuation trial of Study 120 conducted to evaluate the long-term efficacy and safety of PAR in the treatment of panic disorder and to assess the prevention of relapse and recurrence of panic symptoms.
Phase: III
Study Period: February 1993 to September 1994
Study Design: Randomized, double-blind, parallel-group, 6-month study. After completing study 120, subjects who responded and had no significant adverse events could be entered into this study. For the following three months – the "maintenance" phase - patients continued on their previous treatment (placebo; 10mg; 20mg; or 40mg PAR). Patients who were responders (≥50% reduction in number of panic attacks relative to study 120 baseline data) in the last two weeks of the maintenance phase and had not relapsed during the course of the maintenance phase were permitted to enter the second phase – the "re-randomization phase". Patients were re-randomized to either their existing treatment regimen or placebo. The re-randomization phase was of three months duration.
Centre: 18 centers in the United States and Canada
Indication: Panic disorder
Treatment: During the 12-week maintenance phase, patients continued to receive double-blind medication (Placebo [PBO], PAR 10 mg/day, PAR 20 mg/day, or PAR 40 mg/day) based on their previous randomization in Study 120. At the end of this phase, patients were re-randomized to receive for 12 weeks either placebo or the same treatment they received in Study 120 (PBO, PAR 10 mg/day, PAR 20 mg/day, or PAR 40 mg/day). At the end of the 24 weeks treatment phase, patients entered a 4 week run-out period, during which the paroxetine dose was reduced by 10mg increments at weekly intervals. By the beginning of week 28, all patients were dispensed placebo.
Objectives: To assess the efficacy of PAR in preventing relapse of panic disorder and recurrence of panic symptoms To evaluate the long-term efficacy of PAR in the treatment of outpatients with panic disorder and to assess its long-term safety/tolerability
Primary Outcome/Efficacy Variable: The percentage of patients who relapsed in re-randomization phase (defined as the frequency of full panic attacks ≥ frequency observed at baseline in Study 120, and/or an increase of 2 or more points on Clinical Global Impressions (CGI) Severity of Illness from Week 12 visit of maintenance phase) Time to relapse (days) measured from beginning of re-randomization phase
Secondary Outcome/Efficacy Variables: Percentage of patients having zero full panic attacks Mean change from Study 120 baseline in the number of full panic attacks/two weeks in the maintenance phase Mean change from end of maintenance phase in number of full panic attacks/two weeks in re-randomization phase Percentage of patients ≥50% reduction from Study 120 baseline in the number of full panic attacks Mean change from Study 120 baseline in CGI Severity of Illness score at each visit in maintenance phase Mean change from end of maintenance phase in CGI Severity of Illness score at each visit in re-randomization phase.
Statistical Methods: Primary and secondary efficacy analyses were performed on the Intent-to-Treat (ITT) population, which included all patients who received any double-blind medication, entered the maintenance phase, and had at least one valid post-treatment efficacy evaluation. All patients randomized were included in the safety analyses. The efficacy dataset of primary interest was the analysis of ITT population, endpoint dataset. Two datasets were used in the analysis: The observed cases (visit-wise dataset) consisted of each subject's assessment at each visit The endpoint dataset consisted of one observation per patient, that observation being each patient's last observation in the re-randomization phase. The proportion of patients achieving a response per two-week interval, i.e., the proportion relapsing, having zero full panic attacks, and achieving ≥50% reduction in number of full panic attacks was analyzed via the Chi-square test or Fisher's exact test. Due to the small number of subjects who relapsed in the PAR-to-PAR group (2/43), the time to relapse analysis during the re-randomization phase was not done. Mean change in CGI Severity of Illness and additional efficacy variables were analyzed using

parametric analysis of variance methodology. Mean change in the number of full panic attacks and other panic inventory variables were analyzed using the non-parametric Mann Whitney U test. Because approximately 68% treatment by investigator's cells in the re-randomization phase had less than four patients, the investigator term was not included in the model. Where appropriate, analyses were done using only the treatment effect.

All statistical comparisons in the re-randomization phase between treatment groups were two-tailed and performed at the 5% significance level. The primary comparison of interest was the PAR-to-PAR versus the PAR-to-PBO contrast pooled over the three active treatment arms at the end of the re-randomization phase

Sample size estimates were based on the following assumptions: study 120 was designed to have 55 subjects per dose level at the end of 10 weeks of treatment. If 70% of PAR patients met the definition of response, then 115 (=3 x 55 x 0.70) PAR-treated patients would enter the maintenance phase of Study 222. If there were no further premature terminations, then Study 22 would result in over 90% power to detect a difference of 30% (PAR 40%; PBO 70%) in relapse rate in the re-randomization phase.

Study Population: Male or female outpatients, aged ≥18 years, with a clinical diagnosis of panic disorder with or without agoraphobia according to the DSM-III-R criteria (300.21 or 300.01) who completed the final visit (Week 10) of Study 120 and met the criteria for a responder (≥50% reduction in the number of full panic attacks per two weeks relative to Study 120 baseline; or no full panic attacks during latter two week interval) and had no significant adverse events ongoing at the time of entry into this study. Key exclusion criteria included any other axis I disorder, severe or uncontrolled medical condition, pregnant or lactating women or women of child bearing age who did not employ adequate contraception, high risk of suicide, and clinically relevant abnormalities in hematology or clinical chemistry or urinalysis detected at the initial visit.

Number of Subjects:	**PAR 10**	**PAR 20**	**PAR 40**	**PBO**
Completed Study 120, N	45	47	50	46
Maintenance Phase				
Planned, N	38	38	38	-
Entered, n (%)	34 (75.6)	34 (72.3)	40 (80.0)	30 (65.2)
Completed, n (%)	30 (88)	26 (76)	37 (93)	23 (77)
Total Number Subjects Withdrawn*, N (%)	7 (20.6)	8 (23.5)	7 (17.5)	11 (36.7)
Withdrawn due to Lack of Efficacy (LOE)/Relapse n (%)	0 (0)	2 (5.9)	2 (5.0)	4 (13.3)
Withdrawn due to LOE plus AE n (%)	0 (0)	0 (0)	0 (0)	1 (3.3)
Withdrawn due to Total AEs n (%)	1 (2.9)	1 (2.9)	1 (2.5)	1 (3.3)
Withdrawn for Other Reasons n (%)	6 (17.6)	5 (14.7)	4 (10.0)	6 (20.0)

* Includes subjects who did not enter the re-randomization phase.

Re-Randomization Phase	**Entered Re-Randomization**		**Completed Study*** **	
	PBO	**PAR**	**PBO**	**PAR**
Placebo, N	19	0	14	0
Paroxetine 10 mg, N	15	12	9	9
Paroxetine 20 mg, N	13	13	7	9
Paroxetine 40 mg, N	15	18	7	15
Paroxetine Total, N	43	43	23	33

***Completed the randomization phase (week 24)

Re-Randomization Phase	**PBO to PBO**	**PAR 10 to PBO**	**PAR 20 to PBO**	**PAR 40 to PBO**	**PAR 10**	**PAR 20**	**PAR 40**
Total Number Patients Withdrawn, N (%), ITT Population	5 (26.3)	6 (40.0)	6 (46.2)	8 (53.3)	3 (25.0)	4 (30.8)	3 (16.7)
Withdrawn due to Lack of Efficacy (LOE)/Relapse n (%)	0 (0)	1 (6.7)	2 (15.4)	2 (13.3)	0 (0)	1 (7.7)	1 (5.6)
Withdrawn due to LOE plus AE n (%)	0 (0)	0 (0)	2 (15.4)	1 (6.7)	1 (8.3)	1 (7.7)	0 (0)
Withdrawn due to Total AEs n (%)	1 (5.3)	1 (6.7)	3 (23.1)	4 (26.7)	1 (8.3)	1 (7.7)	1 (5.6)
Withdrawn for Other Reasons n (%)	4 (21.1)	4 (26.7)	1 (7.7)	2 (13.3)	2 (16.7)	2 (15.4)	1 (5.6)

Demographics for the Maintenance Phase	**PAR 10**	**PAR 20**	**PAR 40**	**PBO**
ITT Population, N	34	34	40	30
Females: Males	25:9	23:11	23:17	22:8
Mean Age, years (SD)	38.2 (9.9)	34.4 (10.0)	38.4 (10.6)	37.9 (10.8)
Caucasian, n (%)	26 (76.5)	29 (85.3)	37 (92.5)	25 (83.3)
Demographics for the Re-Randomization Phase	**PAR 10**	**PAR 20**	**PAR 40**	**PBO**
ITT Population, N	12	13	18	62
Females: Males	10:2	9:4	11:7	41:21

Mean Age, years (SD)	37.8 (12.9)	34.4 (11.0)	35.3 (10.5)	39.2 (10.1)
Caucasian, n (%)	9 (75.0)	12 (92.3)	17 (94.4)	53 (85.5)

Primary Efficacy Results:

Summary of Relapse During Randomization Phase (ITT Population)

	PAR 10 to PBO	PAR 20 to PBO	PAR 40 to PBO	Total PAR to PBO	PAR 10	PAR 20	PAR 40	PAR Total
Relapse n/N	2/12	2/12	7/13	11/37	0/12	1/13	1/18	2/43
Relapse %	16.7	16.7	53.8	29.7	0.0	7.7	5.6	4.7
Median Days to Relapse	11.0	24.5	13.0	14.0	-	28.0	14.0	21.0
Mean Days to Relapse	11.0	24.5	18.9	18.5	-	28.0	14.0	21.0

Note: Treatment p-value for % relapse PAR versus PBO = 0.002.

Secondary Outcome Variables:

Results shown below present the end of the maintenance phase to study endpoint (end of re-randomization phase) for the secondary outcome variables.

	PBO to PBO		PAR to PBO		PAR Total	
	n	Mean (SE) or %	n	Mean (SE) or %	n	Mean (SE) or %
Number of Full Panic Attacks/2 Weeks						
End of Maintenance Phase*	18	0.64 (0.38)	37	0.15 (0.06)	42	0.37 (0.25)
Change at Endpoint†	18	-0.23 (0.19)	37	2.00 (1.05)	42	0.38 (0.35)
Percentage of Patients with 0 Full Panic Attacks/2 Weeks						
End of Maintenance Phase	13/19	68.4%	35/43	81.4 %	36/42	85.7 %
Endpoint§	13/18	72.2%	27/37	73.0 %	3943	90.7 %
Percentage of Subjects ≥50% Decrease in Number of Full Panic Attacks/2 Weeks						
End of Maintenance Phase	18/19	94.7%	43/43	100.0 %	42/42	100.0 %
Endpoint	18/18	100.0%	30/37	81.1 %	41/43	95.3 %
Number of All Panic Attacks/2 Weeks						
End of Maintenance Phase	-	-	37	1.68 (0.97)	42	1.57 (0.92)
Change at Endpoint	-	-	37	2.34 (1.43)	42	0.39 (0.41)
CGI Severity of Illness						
End of Maintenance Phase	19	2.42 (0.37)	37	1.89 (0.19)	43	2.21 (0.14)
Change at Endpoint	19	0.05 (0.32)	37	0.70 (0.23)	43	-0.05 (0.12)

* Mean value or percentage obtained at end of Maintenance Phase. † Mean change from end of Maintenance Phase at Endpoint. § Percentage at Endpoint.

Safety Results:

Adverse Event incidence in each treatment group is presented as events with onset during the maintenance phase (including events occurring up to 14 days after premature withdrawal from study) and as events with onset during the re-randomization phase (including events occurring up to 14 days after premature withdrawal or after end of run-out phase)

Incidence of Most Frequent Adverse Events with Onset During Maintenance Phase, n (%)

	PBO N=30	PAR 10 N=34	PAR 20 N=34	PAR 40 mg N=40
Subjects with any AE(s) n (%)	24 (80.0)	22 (64.7)	28 (82.4)	32 (80.0)
Asthenia	0 (0.0)	3 (8.8)	2 (5.9)	4 (10.0)
Headache	6 (20.0)	7 (20.6)	8 (23.5)	10 (25.0)
Infection	2 (6.7)	5 (14.7)	6 (17.6)	3 (7.5)

Nausea	3 (10.0)	3 (8.8)	1 (2.9)	4 (10.0)	
Weight Gain	2 (6.7)	2 (5.9)	4 (11.8)	2 (5.0)	
Depression	4 (13.3)	1 (2.9)	0 (0.0)	2 (5.0)	
Dizziness	3 (10.0)	3 (8.8)	0 (0.0)	4 (10.0)	
Insomnia	1 (3.3)	1 (2.9)	4 (11.8)	2 (5.0)	
Respiratory Disorder	6 (20.0)	4 (11.8)	7 (20.6)	4 (10.0)	
Rhinitis	3 (10.0)	0 (0.0)	1 (2.9)	2 (5.0)	
Sinusitis	1 (3.3)	7 (20.6)	4 (11.8)	5 (12.5)	
Sweating	0 (0.0)	1 (2.9)	0 (0.0)	4 (10.0)	

Incidence of Most Frequent Emergent Adverse Events Occurring in Re-Randomization Phase, n (%)

		PAR 10		**PAR 20**		**PAR 40**		**PAR TOTAL**	
	PBO to PBO N=19	**To PBO N=15**	**To PAR 10 N=12**	**To PBO N=13**	**To PAR 20 N=13**	**To PBO N=15**	**To PAR 40 N=18**	**To PBO N=43**	**To PAR Tot. N=43**
Subjects with any AE(s) n (%)	13 (68.4)	9 (60.0)	10 (83.3)	11(84.6)	7(53.8)	10(66.7)	14(77.8)	30(69.8)	31(72.1)
Chest pain	1 (5.3)	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)	5 (11.6)	0 (0.0)
Headache	4 (21.1)	2 (13.3)	0 (0.0)	1 (7.7)	0 (0.0)	6 (40.0)	2 (11.1)	9 (20.9)	2 (4.7)
Infection	3 (15.8)	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)	1 (6.7)	1 (5.6)	3 (7.0)	1 (2.3)
Trauma	1 (5.3)	3 (20.0)	2 (16.7)	2 (15.4)	1 (7.7)	0 (0.0)	0 (0.0)	5 (11.6)	3 (7.0)
Vasodilation	0 (0.0)	1 (6.7)	2 (16.7)	0 (0.0)	0 (0.0)	2 (13.3)	0 (0.0)	3 (7.0)	2 (4.7)
Constipation	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)
Diarrhea	1 (5.3)	2 (13.3)	1 (8.3)	1 (7.7)	0 (0.0)	1 (6.7)	1 (5.6)	4 (9.3)	2 (4.7)
Dyspepsia	2 (10.5)	1 (6.7)	0 (0.0)	2 (15.4)	1 (7.7)	1 (6.7)	0 (0.0)	4 (9.3)	1 (2.3)
Nausea	2 (10.5)	0 (0.0)	2 (16.7)	3 (23.1)	3 (23.1)	3 (20.0)	2 (11.1)	6 (14.0)	7 (16.3)
Weight gain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.1)	0 (0.0)	2 (4.7)
Anxiety	1 (5.3)	1 (6.7)	3 (25.0)	0 (0.0)	1 (7.7)	1 (6.7)	1 (5.6)	2 (4.7)	5 (11.6)
Depersonalization	1 (5.3)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	3 (20.0)	0 (0.0)	3 (7.0)	1 (2.3)
Depression	2 (10.5)	0 (0.0)	1 (8.3)	3 (23.1)	1 (7.7)	3 (20.0)	0 (0.0)	6 (14.0)	2 (4.7)
Dizziness	4 (21.1)	3 (20.0)	5 (41.7)	3 (23.1)	3 (23.1)	2 (13.3)	3 (16.7)	8 (18.6)	11 (25.6)
Emotional lability**	1 (5.3)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.7)	3 (20.0)	0 (0.0)	3 (7.0)	2 (4.7)
Nervousness	0 (0.0)	1 (6.7)	3 (25.0)	0 (0.0)	2 (15.4)	2 (13.3)	0 (0.0)	3 (7.0)	5 (11.6)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (11.1)	1 (2.3)	2 (4.7)
Tremor	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)
Vertigo	1 (5.3)	0 (0.0)	0 (0.0)	2 (15.4)	0 (0.0)	3 (20.0)	0 (0.0)	5 (11.6)	0 (0.0)
Respiratory Disorder	1 (5.3)	0 (0.0)	3 (25.0)	3 (23.1)	1 (7.7)	1 (6.7)	4 (22.2)	4 (9.3)	8 (18.6)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	2 (11.1)	0 (0.0)	2 (4.7)
Otitis Media	0 (0.0)	0 (0.0)	1 (8.3)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.7)	1 (2.3)
Tinnitus	2 (10.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)	1 (2.3)	0 (0.0)

Dysmenorrhea*	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
* Percentages corrected for gender.									

Serious Adverse Events – On DBL Therapy	**PAR**	**PBO**
Subjects with non-fatal SAEs, n [related]	1 [0]	2 [1]
Weakness, dizziness, tight chest, balance problems, difficulty remembering things	0	1 [1]
Cholecystitis (resulting in cholecystectomy)	1 [0]	0 [0]
Bartholin cyst (abdominal pain)	0	1 [0]
Subjects with fatal SAEs, n [related]	0	0

**Term may include: Completed suicides, self harm, suicidal thoughts, attempted suicide, crying and mood fluctuations.

Conclusion:
See publication below.

Publications:

Judge R et al. Paroxetine long-term safety and efficacy in panic disorder and prevention of relapse: a double-blind study. Eur. Psychiatry 1996; 11(Suppl 4):346S

Efficacy and safety of paroxetine in panic disorder. Judge, R 20th Collegium Internationale Neuro-Psychopharmacologicum Congress (CINP '96) 6/23/1996 Melbourne; Australia

The long-term efficacy and safety of paroxetine in panic disorder. Judge, R and Steiner, M 20th Collegium Internationale Neuro-Psychopharmacologicum Congress (CINP '96) 6/23/1996 Melbourne; Australia

Efficacy and safety of paroxetine in panic disorder. Judge, R 8th Congress of the Association of European Psychiatrists/Annual Meeting of the Royal College of Psychiatrists 7/7/1996 London; UK

Paroxetine long-term safety and efficay in panic disorder and prevention of relapse: a double-blind study. Judge, R, Burnham, D, Steiner, M, Gergel, I, Oakes, R, Bailer, D, and Wheadon, D 8th Congress of the Association of European Psychiatrists/Annual Meeting of the Royal College of Psychiatrists 7/7/1996 London; UK

Efficacy and safety of paroxetine in panic disorder. Judge, R 10th World Congress of Psychiatry 8/23/1996 Madrid; Spain

Paroxetine long-term safety and efficacy in panic disorder and prevention of relapse: a double-blind study. Judge, R, Burnham, D, Steiner, M, Gergel, I, Oakes, R, and Bailer, D 10th World Congress of Psychiatry 8/23/1996 Madrid; Spain

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