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.: PAR 470
Title: An Extension Trial Comparing Paroxetine and Placebo in the Long Term Treatment of Generalized Social Phobia
Rationale: Social Phobia has recently been recognized as a distinct anxiety disorder in the psychiatric literature as well as in the fourth edition of the Diagnostic and Statistical Manual, (DSM-IV). The National Comorbidity Study has estimated the prevalence of this disorder as 7.9% for the 12-month frequency rate and 13.3% as the lifetime rate. Social Phobia is characterized by the specific fear of public eating, drinking, or speaking or by fears of more generalized social interactions such as dating or talking to colleagues. This syndrome contributes to functional impairment and diminished quality of life. The Sponsor has conducted an acute placebo (PBO)-controlled, randomized study (Study PAR 382) demonstrating the efficacy and safety of paroxetine in the treatment of acute Social Phobia. The present clinical trial was intended to evaluate the effectiveness of paroxetine in the long-term treatment of Social Phobia.
Phase: III
Study Period: 8 September 1995 to 3 December 1996
Study Design: A two phase study consisting of a 24-week open-label phase followed by a 16 week randomized, PBO-controlled, double-blind phase in subjects who had completed paroxetine social anxiety disorder protocol 382.
Centres: 12 centres in the US
Indication: Generalized Social Phobia
Treatment: Once subjects completed the acute trial, PAR 382, they were eligible to begin the 24-week open-label paroxetine phase of this trial. Subjects who had a Clinical Global Impressions Global Improvement (CGI-I) Item score of 2 or less upon completion of the open-label phase were then randomized to either paroxetine or PBO in the 16-week double-blind phase. This study used a flexible dosage scheme. All subjects entering the open-label phase were to have started at 20mg/day for at least the first 7 days. Thereafter, a weekly dosage elevation of 10mg/day was permitted by investigator's discretion. An increase in daily dosage was not permitted between visits. The maximum daily dosage was 50mg. During the double-blind phase, the subjects randomized to paroxetine remained at the open-label dosage they had achieved by titration in the open label phase. The subjects randomized to PBO entered a blinded gradual down-titration period. The rate was a 10mg reduction at 7 day intervals until dosage level 1 (20 mg) was reached. After dosage level 1 (20 mg) was taken for 7 days, the study medication became PBO for the remainder of the double-blind phase. Gradual reduction of dosage (for those above 20mg/day) was recommended for subjects who completed the trial or who prematurely withdrew. This taper period lasted up to 21 days.
Objectives: The objective of this study was to compare the long-term efficacy of paroxetine and PBO in the treatment of subjects with Generalized Social Phobia.
Primary Outcome/Efficacy Variable: The primary efficacy variable was the proportion of double-blind phase subjects relapsing and the time to relapse during the double-blind PBO-controlled phase of the study. Relapse was defined as a CGI-I Item score greater than 2 for two consecutive visits.
Secondary Outcome/Efficacy Variable(s): Open Label Phase: Proportion of responders on the CGI-I at open label phase completion (Week 24) and open label endpoint. Mean change from baseline to open label phase completion (Week 24) and endpoint in the following: Liebowitz Social Anxiety Scale (LSAS) Total score and both the Fear/Anxiety subscale and Avoidance subscale scores, the Social Avoidance and Distress Scale (SAD) score, and the Sheehan Disability Scale (SDS) work, social life and family life scale scores. Double Blind Phase: Proportion of responders on the CGI-I at week 40 (completion) and endpoint. Mean change from the Week 24 visit (the last open label phase visit, defined as the baseline for the double blind phase) to Week 40 (completion) and endpoint in the following: LSAS Total score and both the Fear/Anxiety subscale and Avoidance subscale scores, the SAD score, and the SDS work, social life and family life scale scores.
Statistical Methods: Time to relapse, measured from the start of the double-blind phase, was analyzed using COX proportional hazards modeling. The proportion of subjects relapsing during the double-blind phase was analyzed using Fishers Exact test. The primary comparison of interest was paroxetine versus PBO during the double-blind phase. All statistical tests were two-sided and were performed at an alpha level of 0.05. The primary population of interest was the Intention-To-Treat (ITT) population, consisting of all subjects who received

double-blind medication for the double-blind phase. All subjects who had at least one valid post-entry efficacy assessment were included in the efficacy analysis.
The efficacy variables were presented in two ways, using the visit-wise dataset and the endpoint dataset. The visit-wise dataset analyzed each observation at the timepoint it was collected, no data were carried forward to estimate missing data points. The endpoint data set used only one observation per subject, the last observation carried forward (LOCF).
Baseline for the double-blind phase was defined as the last open-label phase assessment (Week 24). Baseline for the open-label phase was defined as the baseline of Study 382.
All efficacy variables were summarized during the open-label phase using the visit-wise (at week 24) and endpoint datasets to display the baseline and mean change from baseline scores and proportions observed at the visit intervals.
Data collected during the double-blind phase were summarized using the visit-wise (at week 40) and endpoint datasets to display the mean change from the Week 24 scores and proportion observed at the visit intervals.
No statistical comparisons were done with the open-label phase data.

Study Population: Subjects completing the acute trial, Study PAR 382, were eligible to enter the 24-week open-labeled paroxetine phase of the trial. Subjects who had a CGI-I score of 2 or less at completion of acute study 382 were then randomized to either paroxetine or PBO in the 16-week double-blind phase.

	Open-Label Phase I	**Double-Blind Phase**	
Number of Subjects:	**Open Label Paroxetine**	**Paroxetine**	**PBO**
Planned, N	98	49	49
Entered/Randomized, N	98	27	28
Completed, n (%)	55	21	15
Total Number Subjects Withdrawn, N (%)	43* (43.9)	6 (22.2)	13 (46.4)
Withdrawn due to Adverse Events n (%)	19 (19.4)	2 (7.4)	4 (14.3)
Withdrawn due to Lack of Efficacy n (%)	8 (8.2)	2 (7.4)	3 (10.7)
Withdrawn for other reasons n (%)	16 (16.3)	2 (7.4)	6 (21.4)
*Includes 9 patients who completed the OL phase but did not enter the DB phase.			

Demographics:	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
N (ITT)	98	27	28
Females: Males	37:61	13:14	8:20
Mean Age, years (sd)	35.1 (11.3)	37.2 (11.9)	32.5 (10.5)
White, n (%)	85 (86.7)	23 (85.2)	23 (82.1)

Primary Efficacy Results (ITT):	**Open-Label Phase I**	**Double-Blind Phase**	
Proportion of Relapsers and Time to Relapse Based on CGI-I Item Score (Double-Blind Phase Only)	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, n	-	27	28
Endpoint, n	-	27	27
n (%)	-	8 (29.6)	5 (18.5)
Median Time to Relapse, days	-	11.0	56.0
Mean Time to Relapse, days	-	17.6	46.2
Treatment p-value	-	0.526	

Secondary Outcome Variables (ITT):	**Open-Label Phase I**	**Double-Blind Phase**	
Proportion of Responders Having A CGI-I Score of 1 or 2	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	28
n (%)	44 (48.9)	25 (92.6)	27 (96.4)
Week 24 (Open Label), N	64	-	-
n (%)	57 (89.1)	-	-

Week 40, N	-	22	15
n (%)	-	20 (90.9)	13 (86.7)
Endpoint, N	90	27	28
n (%)	68 (75.6)	22 (81.5)	21 (75.0)
Baseline and Mean Change from Baseline in LSAS Total Score	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27
Mean (sd) for Open Label; (se) for Double-Blind	81.88 (23.8)	30.67 (4.0)	28.27 (4.0)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-48.80 (25.9)	-	-
Week 40, N	-	22	14
Mean Change from Baseline (se)	-	2.64 (3.1)	9.26 (3.9)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-42.29 (28.1)	5.15 (2.8)	7.69 (2.8)
Baseline and Mean Change from Baseline in LSAS Fear/Anxiety Subscale Score	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27
Mean (sd) for Open Label; (se) for Double-Blind	42.42 (11.2)	16.63 (2.1)	15.27 (2.10)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-24.84 (12.2)	-	-
Week 40, N	-	22	14
Mean Change from Baseline (se)	-	1.27 (1.7)	4.84 (2.17)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-21.29 (13.7)	2.59 (1.6)	4.10 (1.6)
Baseline and Mean Change from Baseline in LSAS Avoidance Subscale Score	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27
Mean (sd) for Open Label; (se) for Double-Blind	39.46 (13.4)	14.04 (2.0)	13.00 (2.0)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-23.97 (14.3)	-	-
Week 40, N	-	22	14
Mean Change from Baseline (se)	-	1.36 (1.6)	4.42 (2.0)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-21.00 (15.0)	2.56 (1.4)	3.59 (1.4)
Baseline and Mean Change from Baseline in SAD Total Scores	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27
Mean (sd) for Open Label; (se) for Double-Blind	22.47 (4.6)	9.44 (1.4)	6.30 (1.4)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-13.68 (7.83)	-	-
Week 40, N	-	22	15
Mean Change from Baseline (se)	-	0.09 (1.1)	4.07 (1.3)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-11.98 (7.9)	0.85 (1.1)	4.22 (1.1)
Baseline and Mean Change from Baseline in SDS Work Item Scores	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27

Mean (sd) for Open Label; (se) for Double-Blind	4.90 (2.9)	1.78 (0.3)	1.93 (0.3)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-2.60 (2.3)	-	-
Week 40, N	-	22	15
Mean Change from Baseline (se)	-	0.09 (0.2)	0.87 (0.3)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-2.48 (2.4)	0.44 (0.3)	0.96 (0.3)
Baseline and Mean Change from Baseline in SDS Social Life Item Scores	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27
Mean (sd) for Open Label; (se) for Double-Blind	6.91 (2.4)	2.85 (0.4)	2.56 (0.4)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-4.21 (2.6)	-	-
Week 40, N	-	22	15
Mean Change from Baseline (se)	-	-0.36 (0.3)	0.13 (0.3)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-3.73 (2.6)	-0.07 (0.3)	0.48 (0.3)
Baseline and Mean Change from Baseline in SDS Family Life Item Scores	**Open Label Paroxetine N=98**	**Paroxetine N=27**	**PBO N=28**
Baseline, N	90	27	27
Mean (sd) for Open Label; (se) for Double-Blind	2.99 (2.5)	0.81 (0.3)	1.44 (0.3)
Week 24 Open Label, N	63	-	-
Mean Change from Baseline (sd)	-1.57 (2.2)	-	-
Week 40, N	-	22	15
Mean Change from Baseline (se)	-	-0.05 (0.2)	0.60 (0.2)
Endpoint, N	90	27	27
Mean Change from Baseline (sd) for Open Label; (se) for Double-Blind	-1.34 (2.2)	0.26 (0.2)	0.63 (0.2)

Safety Results: All subjects who were randomly assigned to study medication in the double-blind phase and received at least one dose were included in the ITT safety population. Safety evaluations were conducted for adverse experiences (AE) and vital signs by parameter. AEs were recorded during the treatment phase to within 14 days of last study medication dose and fatal SAEs were recorded up to 30 days following subject completion.

Most Frequent Adverse Events – On-Therapy	**Open-Label Phase I**	**Double-Blind Phase**	
	Open Label Paroxetine	**Paroxetine**	**PBO**
N	98	27	28
	n (%)	**n (%)**	**n (%)**
Subjects with any AE(s)	91 (92.9)	22 (81.5)	23 (82.1)
Headache	28 (28.6)	9 (33.3)	7 (25.0)
Somnolence	27 (27.6)	4 (14.8)	1 (3.6)
Asthenia	19 (19.4)	1 (3.7)	2 (7.1)
Respiratory Disorder	18 (18.4)	2 (7.4)	2 (7.1)
Abnormal Ejaculation -percentage correct for gender	17 (27.9)	1 (7.1)	1 (5.0)
Dizziness	15 (15.3)	2 (7.4)	6 (21.4)
Nausea	14 (14.3)	2 (7.4)	3 (10.7)
Insomnia	13 (13.3)	1 (3.7)	2 (7.1)
Decreased appetite	11 (11.2)	1 (3.7)	0 (0)
Infection	11 (11.2)	0 (0)	1 (3.6)
Nervousness	7 (7.1)	2 (7.4)	7 (25.0)

Constipation	5 (5.1)	2 (7.4)	0 (0)
Anxiety	4 (4.1)	1 (3.7)	4 (14.3)
Diarrhea	4 (4.1)	0 (0)	3 (10.7)
Arthralgia	4 (4.1)	3 (11.1)	2 (7.1)
Sweating	3 (3.1)	3 (11.1)	4 (14.3)
Agitation	3 (3.1)	2 (7.4)	0 (0)
Sinusitis	3 (3.1)	0 (0)	4 (14.3)
Allergic Reaction	2 (2.0)	2 (7.4)	3 (10.7)
Withdrawal Syndrome	2 (2.0)	2 (7.4)	0 (0)
Tooth Disorder	1 (1.0)	3 (7.4)	0 (0)
Concentration Impaired	1 (1.0)	2 (7.4)	1 (3.6)
Depression	1 (1.0)	6 (22.2)	4 (14.3)
Palpitation	0 (0)	2 (7.4)	0 (0)
Emotional lability*	0 (0)	2 (7.4)	3 (10.7)
Ear Pain	0 (0)	2 (7.4)	0 (0)
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	**Open-Label Phase I**	**Double-Blind Phase**	
	Open Label Paroxetine	**Paroxetine**	**PBO**
Subjects with any SAEs, n (%) -Includes both fatal and non-fatal events	1 (1.0)	1 (3.7)	1 (3.6)
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Psychosis	1 (1.0) [0]	0 (0)	0 (0)
Manic Reaction	1 (1.0) [1]		
Overdose (accidental)	0 (0)	1 (3.7) [0]	1 (3.6) [1]
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Subjects with fatal SAEs, n (%)	0 (0)	0 (0)	0 (0)

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

Conclusion:
See publication below.

Publications:

Kumar R et al. Response to paroxetine is maintained during continued treatment in patients with social anxiety disorder. European Neuropsychopharmacology 9(S5): S312 (poster presentation)

Response to paroxetine is maintained during continued treatment in patients with social anxiety disorder. Kumar, R. , Pitts, C. , and Carpenter, D. 12th European College of Neuropsychopharmacology Congress (ECNP) 9/21/1999 London; UK

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