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.: 29060/650
Title: A Study of the Maintained Efficacy and Safety of Paroxetine Versus Placebo in the Long-Term Treatment of Posttraumatic Stress Disorder
Rationale: Posttraumatic stress disorder (PTSD) occurs as the result of exposure to extreme traumatic stress and is clinically characterised by persistent re-experiencing of the traumatic event, chronic avoidance of event reminders, numbing of general emotional responsiveness, and hyperarousal. Symptoms must be present for more than one month (acute PTSD) and result in significant psychosocial distress or disability. If symptoms are present for 3 months or greater, a diagnosis of "chronic" PTSD is conferred. While cognitive and behavioural psychotherapies appear effective for some PTSD subjects, psychotherapy may be ineffective, impractical, or inaccessible for others. The study reported here was a 36-week relapse-prevention study to evaluate the maintained efficacy of paroxetine in the long-term treatment of PTSD by assessing the potential for relapse after discontinuation of 12 weeks of medication and to assess the long-term safety and tolerability of paroxetine in the treatment of PTSD.
Phase: III
Study Period: 03 March 1999 - 17 January 2001
Study Design: This was a 36-week multicentre relapse-prevention study. Following 12 weeks single-blind treatment with paroxetine, responders were randomised (1:1) into a 24 week double-blind comparison of continuing paroxetine or receiving placebo.
Centres: This study was carried out in 35 centres in Canada, Netherlands, UK, France, Israel, Italy, and Finland, distributed as follows: 6 in Canada, 3 in the Netherlands, 2 in the UK, 8 in France, 5 in Israel, 8 in Italy, and 3 in Finland.
Indication: Posttraumatic stress disorder
Treatment: Subjects who fulfilled screening entrance criteria entered a one-week single-blind placebo run-in phase. Subjects who scored 4, 5, 6, or 7 on the Clinical Global Impression (CGI) severity of illness item (i.e., at least moderately ill) and who met the baseline inclusion/exclusion criteria, entered a 12-week single-blind paroxetine flexible dose (20-50 mg/day) treatment phase. Following that phase, subjects whose CGI severity of illness score had decreased by at least two points to a score of 3 or less (i.e., no worse than mildly ill) were classified as responders. Responders were randomised at week 12 to either paroxetine or placebo (1:1 ratio) for a 24-week double-blind treatment phase. A gradual reduction of study medication dose over a period of three weeks was performed for subjects randomised to receive placebo during the double-blind phase to ensure that these subjects received the first dose of placebo medication at the start of week four of the double-blind phase (week 16 of the study). Patients completing or withdrawing from the study had their daily dose of study medication reduced gradually by 10 mg per week over a period of up to 3 weeks such that they received 20mg/day paroxetine (or its matching placebo) for at least a week before stopping study medication.
Objectives: The primary objective of this study was to evaluate the maintained efficacy of paroxetine in the long-term treatment of PTSD by assessing the potential for relapse after discontinuation of medication. The secondary objective was to investigate the long-term safety of paroxetine in the treatment of PTSD.
Primary Outcome/Efficacy Variable: The primary efficacy variable was the proportion of subjects relapsing during the double-blind treatment phase. Relapse was defined as an increase (i.e. deterioration) of at least 2 points to a score of 4 or more relative to the patient's score at week 12 (randomized treatment baseline) on the CGI Severity of Illness, or withdrawal from the study due to lack of efficacy.
Secondary Outcome/Efficacy Variables: The secondary measures of efficacy were: Proportion of subjects with a deterioration in CGI Severity of Illness. (An increase [i.e., deterioration]) of at least 2 points to a score of 4 or above relative to the subject's score at week 12 [randomised treatment baseline] on the CGI Severity of Illness item.) Proportion of subjects withdrawing due to lack of efficacy (LOE). (The percentage of subjects withdrawing due to LOE during the double-blind treatment phase.) Time to relapse. (The time to relapse [in days] from the start of the double-blind treatment phase.) Change from randomised baseline in the Davidson Trauma Scale (DTS) Total and Intrusion, Avoidance/Numbing, and Hyperarousal Clusters scores. Proportion of responders at endpoint based on the CGI Global Improvement item. (Response was defined as a score of 1 [very much improved] or 2 [much improved] on the scale. Non-response was defined as $\geq$3.) Change from randomised baseline in the Clinician Administered Posttraumatic Stress (CAPS-2) Disorder Scale Total,

Re-Experiencing Symptoms, Avoidance and Numbing Symptoms, and Arousal Symptoms scores.
Percentage of subjects scoring ≤7 on the Treatment Outcome Posttraumatic (TOP-8) Stress Disorder Scale at endpoint.
Change from randomised baseline in the Sheehan Disability Scale (SDS) Total and Family, Social, and Work items.
Change from randomised baseline in the Montgomery and Asberg Depression Rating Scale (MADRS).

Statistical Methods: For the primary efficacy variable, analysis of the number of patients who relapsed was based on the number occurring throughout the entire double-blind treatment phase. With the exception of analyses of time to relapse, proportion of patients deteriorating on the CGI Severity of Illness and the proportion of patients withdrawing due to LOE (for which the approach to the primary efficacy variable was used), inferences from the secondary efficacy variables were based on the LOCF data at the protocol defined 36 week endpoint for the Double-Blind ITT population. All hypothesis tests were two-sided. Statistical tests were performed at the 5% level of significance. Binary efficacy variables were analysed using logistic regression with results presented as adjusted odds ratio and 95% confidence intervals. Continuous efficacy variables were analysed using parametric analysis of covariance with results presented as point estimates and 95% confidence intervals for the adjusted mean differences between treatments. For all analyses, primary inferences were obtained from the model adjusted for baseline efficacy measure (where applicable), country group, gender, type of trauma, time since onset of trauma, baseline MADRS score, and age. For time to relapse, comparisons of survival times between treatment groups during the 24-week double-blind treatment phase were made using a non-parametric log-rank test.

Study Population: This study enrolled subjects with a primary diagnosis of PTSD according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as determined by a full psychiatric interview using the Clinician Administered PTSD Scale - 1 (CAPS-1), with a duration of illness of at least three months, and who had given written informed consent prior to any specific study procedures.
Subjects were at least 18 years old; subjects over 65 years of age had to be able to tolerate a paroxetine starting dose of 20 mg daily and be without renal or hepatic impairment (lab tests at screening had to be within twice the upper limit of normal).
Subjects were excluded from the study if they:
Scored <50 on the CAPS-2 at baseline.
Were diagnosed with Axis I disorders such as dysthymia, simple phobia, Major Depression, Obsessive Compulsive Disorder (OCD), or panic disorder as a primary diagnosis within the 6 months prior to the screening visit.
Presented with a current major depressive episode that preceded the diagnosis of PTSD.
Had a score on the CGI (Severity of Illness item) that decreased by two points or more between screening and baseline or was 1, 2, or 3 at baseline.
In the opinion of the investigator, were likely to exaggerate or falsify the symptoms of PTSD or other related psychiatric disorders for financial or personal gain.
Had a placebo run-in medication compliance of less than 80% or greater than 120% at the baseline visit.
Had clinically significant abnormal laboratory or electrocardiogram (ECG) findings that were not resolved by the baseline (Day 0) examinations.
Had taken other psychotropic drugs that had not been discontinued within the minimum discontinuation periods prior to baseline.
Were using any herbal psychoactive treatments (e.g. St. John's Wort, Valerian).
Had used an investigational drug within 3 months prior to screening (or 5 half-lives, whichever is longer), or 16 weeks in Ireland.
Had had electroconvulsive therapy (ECT) in the three months prior to screening.
Had exhibited intolerance to paroxetine or any other SSRI.
Had received formal psychotherapy concurrently or in the 12 weeks prior to screening.
Met DSM-IV criteria for substance abuse (alcohol or drugs) or substance dependence within 6 months prior to screening.
Posed a current suicide risk.
Had participated in any previous PTSD studies involving paroxetine.
In the investigator's opinion, would have been unable to comply with study procedures or assessments.

Number of Subjects:	**Paroxetine**	**Placebo**
Planned (to be screened),N	306	
Screened, N	300	
Entered in Single-Blind Phase, N	265	
Randomised in Double-Blind Phase, N	88	88
Double-Blind ITT	87	86
Completed (Double-Blind Phase), n (%)	67 (77.0)	63 (73.3)

Total Number Subjects Withdrawn (in Double-Blind Phase), N (%)	20 (23.0)	23 (26.7)
Withdrawn Due to Adverse Events, n (%)	3 (3.4)	4 (4.7)
Withdrawn Due to Lack of Efficacy, n (%)	8 (9.2)	8 (9.3)
Withdrawn for Other Reasons, n (%)	9 (10.3)	11 (12.8)
Demographics – Double-Blind Phase	**Paroxetine**	**Placebo**
N (ITT)	87	86
Females:Males	58:29	56:30
Mean Age, Years (SD)	42.7 (13.9)	42.8 (12.0)
White, n (%)	83 (95.4)	84 (97.7)
Primary Efficacy Results for ITT Population:		
Relapsers During the Double-Blind Treatment Phase	**Paroxetine**	**Placebo**
N	87	86
Relapsers, n (%)	9 (10.3)	11 (12.8)
Odds Ratio	0.65	
95% Confidence Interval (CI)	0.2, 1.8	
p-Value	0.411	
Secondary Efficacy Results for ITT Population:		
Deterioration in CGI Severity of Illness	**Paroxetine**	**Placebo**
N	87	86
Deteriorators, n (%)	9 (10.3)	11 (12.8)
Odds Ratio	0.65	
95% CI	0.2, 1.8	
Withdrawal Due to Lack of Efficacy	**Paroxetine**	**Placebo**
N	87	86
Withdrawal, n (%)	8 (9.2)	8 (9.3)
Odds Ratio	0.82	
95% CI	0.3, 2.5	
Time to Relapse	**Paroxetine**	**Placebo**
N	86	85
Time to Relapse	No evidence of a difference between groups	
Chi-Square	0.360	
Degrees of Freedom	1	
DTS Total	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	85	86
Baseline Mean (SE)	25.9 (2.1)	25.0 (1.8)
N for Week 36 Last Observation Carried Forward (LOCF)	81	78
Mean Change from Baseline to Week 36 LOCF (SE)	-5.5 (1.8)	-3.0 (2.6)
Difference: Paroxetine vs. placebo	-2.9	
95% CI	-9.2, 3.4	
DTS Intrusion	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	85	86
Baseline Mean (SE)	7.8 (0.7)	7.0 (0.6)
N for Week 36 LOCF	81	78
Mean Change from Baseline to Week 36 LOCF (SE)	-2.0 (0.7)	-1.2 (0.9)
Difference: Paroxetine vs. Placebo	-0.7	
95% CI	-2.8, 1.5	
DTS Avoidance	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	86	86
Baseline Mean (SE)	9.7 (0.9)	9.9 (0.9)
N for Week 36 LOCF	82	78
Mean Change from Baseline to Week 36 LOCF (SE)	-1.9 (0.8)	-0.8 (1.1)
Difference: Paroxetine vs. Placebo	-1.5	
95% CI	-4.1, 1.2	
DTS Hyperarousal	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	86	86

Baseline Mean (SE)	8.6 (0.8)	8.1 (0.7)
N for Week 36 LOCF	82	78
Mean Change from Baseline to Week 36 LOCF (SE)	-1.4 (0.8)	-1.0 (0.8)
Difference: Paroxetine vs. Placebo	-0.5	
95% CI	-2.7, 1.7	
Proportion of Responders Based on the CGI Global Improvement Item	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Responders at Week 12 Baseline, n (%)	79 (90.8)	82 (95.4)
N for Week 36 LOCF	86	85
Responders at Week 36 LOCF, n (%)	69 (80.2)	68 (80.0)
Odds Ratio	1.11	
95% CI	0.5, 2.5	
CAPS-2 Total Score	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	23.6 (1.8)	23.8 (1.8)
N for Week 36 LOCF	86	85
Mean Change from Baseline to Week 36 LOCF (SE)	-4.5 (1.9)	-3.3 (2.3)
Difference: Paroxetine vs. Placebo	-1.9	
95% CI	-7.6, 3.8	
CAPS-2 Re-Experiencing Symptoms	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	7.3 (0.6)	6.8 (0.6)
N for Week 36 LOCF	86	85
Mean Change from Baseline to Week 36 LOCF (SE)	-2.0 (0.7)	-1.1 (0.8)
Difference: Paroxetine vs. Placebo	-0.8	
95% CI	-2.8, 1.1	
CAPS-2 Avoidance and Numbing	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	9.1 (0.9)	9.4 (0.8)
N for Week 36 LOCF	86	85
Mean Change from Baseline to Week 36 LOCF (SE)	-1.8 (0.8)	-1.2 ().9)
Difference: Paroxetine vs. Placebo	-0.9	
95% CI	-3.3, 1.5	
CAPS-2 Hyperarousal	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	7.3 (0.7)	7.7 (0.7)
N for Week 36 LOCF	86	85
Mean Change from Baseline to Week 36 LOCF (SE)	-0.8 (0.8)	-1.0 (0.8)
Difference: Paroxetine vs. Placebo	-0.2	
95% CI	-2.2, 1.8	
Responders for TOP-8 Scale	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	85
Responders, n (%)	55 (63.2)	62 (72.9)
N for Week 36 LOCF	83	78
Responders, n (%)	60 (72.3)	56 (71.8)
LOCF Difference	1.21	
LOCF 95% CI	0.6, 2.7	
SDS Total	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	63	68
Baseline Mean (SE)	6.5 (0.8)	7.5 (0.8)
N for Week 36 LOCF	60	58
Mean Change from Baseline to Week 36 LOCF (SE)	-0.2 (0.7)	0.5 (1.0)
Difference: Paroxetine vs. Placebo	-1.5	

95% CI	-3.8, 0.8	
SDS Family	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	2.1 (0.2)	2.1 (0.2)
N for Week 36 LOCF	83	78
Mean Change from Baseline to Week 36 LOCF (SE)	-0.1 (0.2)	0.0 (0.3)
Difference: Paroxetine vs. Placebo	-0.2	
95% CI	-0.9, 0.4	
SDS Social	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	2.4 (0.2)	2.5 (0.3)
N for Week 36 LOCF	83	78
Mean Change from Baseline to Week 36 LOCF (SE)	-0.3 (0.2)	0.0 (0.3)
Difference: Paroxetine vs. Placebo	-0.5	
95% CI	-1.1, 0.2	
SDS Work	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	63	68
Baseline Mean (SE)	2.4 (0.4)	2.8 (0.4)
N for Week 36 LOCF	60	58
Mean Change from Baseline to Week 36 LOCF (SE)	-0.1 (0.3)	0.1 (0.4)
Difference: Paroxetine vs. Placebo	-0.5	
95% CI	-1.4, 0.4	
MADRS Scale	**Paroxetine**	**Placebo**
N for Double-Blind (Week 12) Baseline	87	86
Baseline Mean (SE)	7.8 (0.7)	7.8 (0.7)
N for Week 36 LOCF	83	78
Mean Change from Baseline to Week 36 LOCF (SE)	-0.6 (0.8)	-0.5 (1.0)
Difference: Paroxetine vs. Placebo	-0.6	
95% CI	-2.9, 1.8	
Safety Results: On-therapy adverse events (AEs) were defined as all AEs where the onset date was on or after the first day of treatment and before or on the last day of treatment. All serious adverse events (SAEs) are presented, including those that occurred on treatment or within 30 days following the end of treatment.		
Most Frequent Adverse Events – On-Therapy: Single-Blind Phase	**Paroxetine**	
N	263	
	N (%)	
Subjects with any AE(s)	118 (44.9)	
Nausea	32 (12.2)	
Abnormal Ejaculation (percentage corrected for gender)	10 (9.7)*	
Insomnia	25 (9.5)	
Somnolence	24 (9.1)	
Headache	19 (7.2)	
Impotence (percentage corrected for gender)	7 (6.8)*	
Asthenia	14 (5.3)	
Sweating	11 (4.2)	
Tremor	11 (4.2)	
Abdominal Pain	8 (3.0)	
Constipation	8 (3.0)	
Respiratory Disorder	8 (3.0)	
Most Frequent Adverse Events – On-Therapy: Double-Blind Phase	**Paroxetine**	**Placebo**
N	87	86
	n (%)	**n (%)**
Subjects with any AE(s)	37 (42.5)	28 (32.6)

Headache	5 (5.7)	2 (2.3)
Insomnia	5 (5.7)	2 (2.3)
Pain	4 (4.6)	0
Somnolence	4 (4.6)	0
Anxiety	3 (3.4)	2 (2.3)
Infection	3 (3.4)	4 (4.7)
Trauma	3 (3.4)	1 (1.2)
Weight Gain	3 (3.4)	1 (1.2)
Abnormal Dreams	2 (2.3)	1 (1.2)
Asthenia	2 (2.3)	2 (2.3)
Back Pain	2 (2.3)	1 (1.2)
Dizziness	2 (2.3)	3 (3.5)
Dyspepsia	2 (2.3)	0
Rectal Haemorrhage	2 (2.3)	0
Respiratory Disorder	2 (2.3)	0
Sweating	2 (2.3)	0
Vertigo	2 (2.3)	2 (2.3)
Abdominal Pain	1 (1.1)	2 (2.3)
Agitation	1 (1.1)	2 (2.3)
Nausea	0	3 (3.5)
Ear Pain	0	2 (2.3)
Hypertension	0	2 (2.3)
Nervousness	0	2 (2.3)
Paraesthesia	0	2 (2.3)

Serious Adverse Events for ITT Population
n (%) [n considered by the investigator to be related to study medication]

	Single-Blind Phase	**Double-Blind Phase**	
	Paroxetine	**Paroxetine**	**Placebo**
N	263	87	86
Subjects with Non-Fatal SAEs	5 (1.9)	6 (6.9)	2 (2.3)
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Chest Pain	2 (0.8) [0]	0	0
Cerebrovascular Disorder	1 (0.4) [0]	1 (1.1) [0]	0
Hypertension	1 (0.4) [0]	0	0
Depression	1 (0.4) [0]	0	0
Endometrial Disorder (percentage corrected for gender)	1 (0.6) [0]]	0	0
Unintended Pregnancy (percentage corrected for gender)	1 (0.6) [0]	0	0
Back Pain	0	1 (1.1) [0]	0
Trauma	0	2 (2.3) [0]	0
Extrasystoles	0	1 (1.1) [0]	0
Myocardial Ischemia	0	1 (1.1) [0]	0
Vascular Anomaly	0	1 (1.1) [0]	0
Gastritis	0	0	1 (1.2) [0]
Vomiting	0	1 (1.1) [0]	0
Withdrawal Syndrome (Alcohol)	0	0	1 (1.2) [0]
Subjects with Fatal SAEs	1 (0.4) [0]	0	0
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Emotional Lability*	1 (0.4) [0]	0	0

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

Conclusion: The primary objective of this study was to evaluate the maintained efficacy of paroxetine in the long-term treatment of PTSD by assessing the potential for relapse after discontinuation of medication. However, the primary and all secondary efficacy variables failed to show any statistically significant advantage to maintaining paroxetine treatment. The results from this study show that continuing paroxetine had no bearing on the proportion of subjects who relapsed. However, the proportion of patients that relapsed after responding to single-blind paroxetine treatment was very low in both treatment groups.
Publications: No publication

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