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 29060.07.001
Title: A Double-Blind Comparison of Paroxetine, Amitriptyline, and Placebo in Inpatients with Major Depressive Disorder with Melancholia
Rationale: In animal models paroxetine does not cause overt stimulation or depression, and its peripheral anticholinergic properties are weak. This report summarizes the safety and efficacy data collected from 38 subjects who received paroxetine, amitriptyline, or placebo (PBO) according to the requirements of Protocol PAR 07.
Phase: II
Study Period: October 1986 - August 1987 (due to low subject enrollment, this study was stopped early)
Study Design: Multi-center, 6 week, double-blind, randomized, parallel-group, PBO- and amitriptyline-controlled trial.
Centres: Three centres in the United States
Indication: Major Depressive Disorder with melancholia
Treatment: After successfully completing the screen examinations and a minimum run-in period of 4 days, subjects received two bottles of screen medication (a morning and an evening bottle) and were instructed to take two capsules from each bottle morning and evening. Upon acceptance into the active phase of the study, subjects received morning and evening bottles of study medication and were to take two capsules from each bottle morning and evening. The morning bottles for the paroxetine-treated subjects contained 10mg paroxetine capsules, and the evening bottles contain PBO capsules. The morning and evening bottles for subjects in the amitriptyline treatment group contained 25mg amitriptyline capsules. Between day 3 and day 42, the investigator could use his discretion in increasing or decreasing the dosage (10 to 60mg dose range), to achieve maximum therapeutic benefit. Subjects were then down-titrated between days 43 and 56.
Objectives: The objective of this study was to compare the safety and efficacy of paroxetine as an antidepressant with amitriptyline and PBO in the treatment of subjects with moderately severe to severe major depressive disorder with melancholia, as described in the Diagnostic and Statistical Manual of Mental Disorders 3rd edition (DSM-III).
Primary Outcome/Efficacy Variable: The primary measures of efficacy response in these studies were the 21-item Hamilton Scale for Depression (HAMD-21) Total Score, Symptom Checklist (SCL) Depression Factor, Clinical Global Impressions (CGI) Severity of Illness, and the Montgomery-Asberg Depression Rating Scale (MADRS). Endpoint identified as Week 6.
Secondary Outcome/Efficacy Variable(s): None listed.
Statistical Methods: The primary analysis of the study is based on the All Efficacy Subject population using the extender data set and analysis of variance. The one-way analysis of variance (ANOVA) was of the forms Value = Treatment + Error, or Difference = Treatment + Error. The first form is used to test for treatment group comparability at baseline and to test for treatment group differences during the study in the variables that were not measured at baseline. The second form is used to test the treatment group comparability of change from baseline data of all other efficacy variables (except for the individual HAMD-21 items). Analysis of covariance (ANCOVA) is used to determine if any covariates are important in modeling treatment group response. This model has the form Difference in HAMD-21 Total x Treatment + Covariable + Treatment-by-Covariable + Error. For ordinal data, Cochran-Mantel-Haenszel row means scores methodolgy was used. Fisher's Exact Permutation Test for 2x2 tables is used to test homogeneity of response between treatment groups for analyses relating to demography, psychiatric history, adverse experience rates, and other data measured on a nominal scale. All p-values quoted in this report are based on two-tailed tests. For the primary hypothesis test of

equal paroxetine and PBO means, a p-value of < 0.05 is declared significant.
The Intent-To-Treat Population (ITT) consisted of subjects who were evaluable for safety analysis. These subjects must have entered the active treatment phase of the study, taken double-blind medication, and at least had an opportunity to report the presence or absence of an adverse event (AE).

Study Population: Inpatients, aged 18 years or older, diagnosed with moderately severe to severe major depressive disorder with melancholia (Diagnostic and Statistical Manual of Mental Disorders 3rd edition [DSM-III]), characterized by disorder of mood with symptoms such as depressed mood, sadness, hopelessness, and worthlessness, were eligible for the study.

In addition to the DSM-III diagnostic criteria, subjects had to meet the following inclusion criteria to be eligible:

1. A HAMD-21 score at the baseline visit of at least 21 on the first 17 items, and the HAMD-21 total could not decrease by 20% or more between the screen and baseline visits.
2. A Raskin Depression Scale score at baseline of at least 10, and the Raskin score had to be higher than the Covi Anxiety Scale score (i.e., the subject had to have a higher degree of depression than anxiety to be included in the study).

Key Exclusion Criteria:

1. Subjects with the following psychiatric diagnoses: primary diagnosis of schizophrenia, atypical depressive type, anxiety as the primary disorder, disorders of adjustment, and manic depressive illness.
2. Subjects requiring concomitant therapy with other psychotropic drugs.
3. Subjects who were known to have abused alcohol or drugs within the past 6 months.
4. Subjects who had had electroconvulsive therapy (ECT) within the 3 months preceding baseline, other investigational drugs within 30 days preceding baseline, monoamine oxidase inhibitors within 14 days preceding baseline, or other psychotropic drugs within 4 days preceding baseline.
5. Subjects who were serious suicidal risks.
6. Women with a positive pregnancy test
7. Lactating females and women of childbearing potential who were not practicing a medically accepted form of birth control.

	Paroxetine	**Amitriptyline**	**PBO**
Number of Subjects:	13	13	12
Planned, N	120		
Randomized, N	13	13	12
ITT, N	13	13	12
Completed, n (%)	8 (62)	11 (85)	7 (58)
Total Number Subjects Withdrawn, N (%)	5 (38)	2 (15)	5 (42)
Withdrawn due to Adverse Events n (%)	1 (8)	2 (15)	2 (17)
Withdrawn due to Lack of Efficacy n (%)	4 (31)	0	2 (17)
Withdrawn for other reasons n (%)	0	0	1 (8)
Demographics:	**Paroxetine**	**Amitriptyline**	**PBO**
N (ITT)	13	13	12
Females: Males	9:4	8:5	5:7
Mean Age, years (SD)	40.0(na)	44.6(na)	45.1(na)
White, n (%)	12 (92)	13 (100)	12 (100)

Primary Efficacy Results(ITT):

HAMD-21 Total Score Mean (s.e.) Improvements From Baseline (Extender Data Set)	**Paroxetine N=13**	**Amitriptyline N=13**	**PBO N=12**
Baseline Mean Score (se)	n=13 30.5 (1.2)	n=13 30.4 (1.2)	n=12 28.3 (1.3)
Week 6 Endpoint Mean change from baseline	n=12 -13.08 (2.95)	n=13 -13.31 (2.83)	n=11 -10.91 (3.08)
Pairwise Comparisons	Paroxetine vs. PBO	Paroxetine vs. Amitriptyline	Amitriptyline vs. PBO
p-value	0.613	0.957	0.570
SCL Depression Factor Score Mean (s.e.) Improvements from Baseline (Extender Data Set)	**Paroxetine N=13**	**Amitriptyline N=13**	**PBO N=12**
Baseline Mean Score (se)	n=13 37.9 (1.8)	n=13 35.3 (1.9)	n=12 34.6 (1.9)
Week 6 Endpoint Mean change from baseline (se)	n=12 -9.33 (2.69)	n=12 -6.33 (2.69)	n=11 -5.01 (2.81)
Pairwise Comparisons	Paroxetine vs. PBO	Paroxetine vs. Amitriptyline	Amitriptyline vs. PBO
p-value	0.275	0.437	0.736
MADRS Scores Mean (s.e.) Improvements from Baseline (Extender Data Set)	**Paroxetine N=13**	**Amitriptyline N=13**	**PBO N=12**
Baseline Mean Score (se)	n=13 33.0 (1.7)	n=13 32.3 (1.7)	n=12 29.9 (1.8)
Week 6 Endpoint Mean change from baseline (se)	n=12 -13.50 (3.20)	n=13 -14.69 (3.07)	n=11 -11.09 (3.34)
Pairwise Comparisons	Paroxetine vs. PBO	Paroxetine vs. Amitriptyline	Amitriptyline vs. PBO
p-value	0.606	0.790	0.433
CGI Severity of Illness Scores Mean (s.e.) Improvements from Baseline (Extender Data Set)	**Paroxetine N=13**	**Amitriptyline N=13**	**PBO N=12**
Baseline Mean Score (se)	n=13 5.1 (0.2)	n=13 5.1 (0.2)	n=12 4.6 (0.2)
Week 6 Endpoint Mean change from baseline (se)	n=12 -1.75 (0.41)	n=13 -1.62 (0.40)	n=11 -1.27 (0.43)
Pairwise Comparisons	Paroxetine vs. PBO	Paroxetine vs. Amitriptyline	Amitriptyline vs. PBO
p-value	0.430	0.816	0.563
Secondary Outcome Variable(s): None			
Safety Results:. AEs that had an onset and stop date prior to the date of first dose of double-blind medication are excluded from the On-Therapy analysis.			

Most Frequent Adverse Events* -On-Ther apy	**Paroxetine N=13**	**Amitriptyli ne N=13**	**PBO N=12**
Subjects with any AE(s), n (%)	12 (92)	12 (92)	9 (75)
Nausea	6 (46)	5 (38)	1 (8)
Somnolence	5 (38)	5 (38)	2 (17)
Decreased Appetite	4 (31)	0	1 (8)
Diarrhea	4 (31)	0	1 (8)
Insomnia	3 (23)	0	3 (25)
Constipation	2 (15)	2 (15)	1 (8)
Dizziness	2 (15)	4 (31)	0
Tremor	2 (15)	6 (46)	1 (8)
Dry Mouth	1 (8)	10 (77)	1 (8)
Headache	1 (8)	4 (31)	4 (33)
Vomiting	1 (8)	2 (15)	1 (8)
Blurred Vision	0	2 (15)	0
Dyspepsia	0	3 (23)	1 (8)
Hypertension	0	2 (15)	0
*any AE that occurs in more than one subject in any group			
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]	**Paroxetine N=13**	**Amitriptyli ne N=13**	**PBO N=12**
Subjects with any SAEs, n (%) -Includes both fatal and non-fatal events	2 (15)	0	0
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Acute Depressive Symptoms/ Suicide Ideation	1(8)[Not specified]	0	0
Acute alcohol intoxication and suicide ideation	1 (8) [not specified]		
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Subjects with fatal SAEs, n (%)	0	0	0

Conclusion: No conclusion can be drawn from this study because of the small number of subjects involved.
Publications: No publication

Date updated: 22-May-2008