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.: NKF100096
Title: A Randomised, Double-Blind, Double-Dummy, Parallel-Group, Placebo-Controlled, Forced Dose Titration Study Evaluating the Efficacy and Safety of a New Chemical Entity (NCE) and Paroxetine in Subjects with Major Depressive Disorder
Rationale The purpose of this study was to evaluate the efficacy and safety of an NCE in outpatients diagnosed with Major Depressive Disorder (MDD). This summary includes data for the paroxetine and placebo groups. Results for the unmarketed NCE will be added, if and when the NCE is approved and marketed.
Phase: II
Study Period: 16 June 2005 to 29 August 2006
Study Design A multicentre, randomized, double-blind, parallel-group, placebo-controlled, forced-dose titration study
Centres: This was a multicentre study performed in 37 centres in Argentina (n = 3), Belgium (n = 4), Chile (n = 4), Costa Rica (n = 3), Germany (n = 7), Italy (n = 4), Peru (n = 1), Poland (n = 3), Slovakia (n = 6), Spain (n = 1) and Sweden (n = 1).
Indication: Major Depressive Disorder (MDD)
Treatment: After completion of a screening period, subjects fulfilling the inclusion/exclusion criteria were randomized (1:1:1) to an NCE, placebo, or paroxetine (20-30mg/day). Clinical supplies of paroxetine consisted of a white to off white powder and an oval shaped film coated tablet contained in a DB-AA size capsule comprised of an opaque Swedish orange body and cap. Overencapsulated SEROXAT™ Tablet strengths of 20mg and 30mg were supplied. Placebo capsules to match were also supplied. Subjects receiving 30mg paroxetine upon completion of treatment or at early withdrawal entered a one-week taper phase during which subjects received 20mg paroxetine.
Objectives: The primary objective of this study was to evaluate the antidepressant efficacy of an NCE versus placebo, in subjects with MDD.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was the change from baseline in the 17-item Hamilton Depression Rating Scale (HAM-D) total score at the Week 8 Last Observation Carried Forward (LOCF) endpoint.
Secondary Outcome/Efficacy Variables The secondary endpoints included the percentage of: subjects with a ≥ 50% reduction from baseline in HAM-D total score (HAM-D responders); subjects with HAM-D total score ≤ 7 (HAM-D remitters) and subjects with Clinical Global Impression- Global Improvement (CGI-I) score of 1 or 2, 'very much improved' or 'much improved' (CGI responders). Change from baseline in the Clinical Global Impression-Severity of Illness (CGI-S) score; the HAM-D item 1 (depressed mood) score; the Hamilton Anxiety Rating Scale (HAM-A) total score; the HAM-A psychic anxiety sub-scale score (sum of items 1, 2, 3, 4, 5, 6 and 14); the HAM-A somatic anxiety sub-scale score (sum of items 7, 8, 9, 10, 11, 12 and 13); the HAM-D anxiety factor score (sum of items 10, 11, 12, 13, 15 and 17); the 16-item Quick Inventory of Depressive Symptomatology (QIDS-SR 16); item 5 (feeling sad) of the QIDS-SR 16; the Sheehan Disability Scale (SDS) total and sub-scale scores; the Medical Outcomes Study (MOS) 12-item Sleep Module (sum of 9 items); the Leeds Sleep Evaluation Questionnaire (LSEQ) "Getting to Sleep", "Quality of Sleep", "Awakening from Sleep" and "Behaviour Following Wakefulness" sub-scale scores and an assessment of satisfaction with study medication.
Statistical Methods: The primary population of interest for efficacy and safety evaluations was the intent-to-treat (ITT) population which consisted of all subjects who gave informed consent, were randomized, received at least one dose of double-blind medication and for whom at least one post-baseline assessment was available. The primary comparison of interest was NCE versus placebo for the primary efficacy endpoint – change from baseline to Week 8 in the 17-item HAM-D total score using a two-sided hypothesis test performed at the 5% level of significance. The results of the analysis were presented as a point estimate, a 95% confidence interval (CI) and an associated p-value for the adjusted mean difference between treatments at every visit.
Study Population: Male and female outpatients between the ages of 18 to 64 years inclusive with a primary diagnosis of a Major Depressive Episode (MDE) associated with MDD according to DSM-IV-TR (296.2 or 296.3) were enrolled into this study. Subjects were required, in the investigator's opinion based on the subject's history, to have met DSM-IV-TR criteria for their current MDE for at least 8 weeks prior to the Screening Visit. Subjects were required to attain a Carroll Depression Scale-Revised (CDS-R) self-assessment total score of ≥24 at the Screen Visit and Baseline Visit and a CGI- Severity of Illness score of ≥ 4 at the Baseline Visit. Medical history, laboratory assessments and ECG results were reviewed to ensure subjects had no clinically significant findings that might preclude the administration of either the NCE or paroxetine.

	Placebo	Paroxetine
Number of Subjects:		
Planned, N	116	116
Randomised, N	123	113
ITT, N	123	109
Subject Completion and Withdrawal (ITT Population):		
Completed, n (%)	88 (72%)	79 (72%)
Total Number Subjects Withdrawn, n (%)	35 (28%)	30 (28%)
Withdrawn due to Adverse Events n (%)	12 (10%)	16 (15%)
Withdrawn due to Lack of Efficacy n (%)	4 (3%)	0
Withdrawn for other reasons n (%)	19 (15%)	14 (13%)
Demographics	Placebo	Paroxetine
N (ITT)	123	109
Females: Males	89:34	80:29
Mean Age, years (SD)	44.0 (10.7)	43.5 (11.4)
Not Hispanic/Latino, n (%)	80 (65%)	71 (65%)
Primary Efficacy Results: This summary includes data for paroxetine and placebo groups. Results for the unmarketed NCE will be added, if and when the NCE is approved and marketed.		
	Placebo (N = 123)	Paroxetine (N = 109)
Change from baseline in HAM-D Total Score at Week 8 LOCF (ITT Population)		
Baseline, mean (SD)	22.5 (5.87)	22.8 (5.47)
Change from baseline, Adjusted mean (Standard Error [SE)])	-11.6 (0.78)	-12.8 (0.83)
Difference versus placebo	NA	-1.2
95% CI	NA	-3.4, 1.0
p-value	NA	0.282
Secondary Outcome Variable(s):		
	Placebo (N = 123)	Paroxetine (N = 109)
Change from baseline in HAM-D Item 1 at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.2
95% CI	NA	-0.5, 0.1
Proportion of HAM-D Responders at Week 8 LOCF (ITT Population)		
Adjusted Odds Ratio	NA	1.01
95% CI	NA	0.59, 1.74
Proportion of HAM-D Remitters at Week 8 LOCF (ITT Population)		
Adjusted Odds Ratio	NA	1.80
95% CI	NA	1.04, 3.11
Change from baseline on CGI Severity of Illness at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.4
95% CI	NA	-0.8, 0.0
CGI Global Improvement Responders at Week 8 LOCF (ITT Population)		
Adjusted Odds Ratio	NA	1.64
95% CI	NA	0.94, 2.86
Change from baseline in HAM-D Anxiety Factor Sub-scale at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.3
95% CI	NA	-1.1, 0.5
Change from baseline in HAM-A Total Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-1.6
95% CI	NA	-3.9, 0.7
Change from baseline in HAM-A Psychic Anxiety Sub-scale Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-1.0
95% CI	NA	-2.3, 0.4
Change from baseline in HAM-A Somatic Anxiety Sub-scale Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.7

95% CI	NA	-1.7, 0.4
Change from baseline in QIDS-SR 16-Item Scale Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-1.2
95% CI	NA	-2.8, 0.4
Change from baseline in QIDS-SR Item 5 (Feeling Sad) Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.3
95% CI	NA	-0.6, 0.0
Change from baseline in SDS Total Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-2.4
95% CI	NA	-4.7, -0.1
Change from baseline in SDS Work Item Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.8
95% CI	NA	-1.6, 0.0
Change from baseline in SDS Family Item Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.8
95% CI	NA	-1.6, 0.0
Change from baseline in SDS Social Item Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-0.7
95% CI	NA	-1.6, 0.1
Change from baseline in Medical Outcomes Study 12-Item Sleep Module (MOS-12) Index II Score at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	2.0
95% CI	NA	-4.0, 7.9
Change from baseline in LSEQ "Getting to Sleep" Item at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-1.1
95% CI	NA	-6.7, 4.5
Change from baseline in LSEQ "Quality of Sleep" Item at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	-5.4
95% CI	NA	-14.2, 3.5
Change from baseline in LSEQ "Awakening from Sleep" Item at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	3.5
95% CI	NA	-3.1, 10.0
Change from baseline in LSEQ "Behaviour Following Wakefulness" Item at Week 8 LOCF (ITT Population)		
Difference versus placebo	NA	0.0
95% CI	NA	-7.2, 7.2
Analysis of Satisfaction with Study Medication Responders at Week 8 LOCF (ITT Population)		
Adjusted Odds Ratio	NA	1.50
95% CI	NA	0.84, 2.69
Safety Results: An on-therapy adverse event (AE) was defined as an AE with onset on or after the start date of study medication but not later than one day after the last date of study medication. An on-therapy serious adverse event (SAE) was defined as a SAE with onset on or after the start date of study medication and up to 30 days after the last dose of medication. This summary includes data for the paroxetine and placebo groups. Results for the unmarketed NCE will be added, if and when the NCE is approved and marketed		
	Placebo (N = 123)	Paroxetine (N = 109)
Most Frequent Adverse Events – On-Therapy	n (%)	n (%)
Subjects with any AE(s), n(%)	82 (67%)	86 (79%)
Headache	32 (26%)	28 (26%)
Nausea	14 (11%)	31 (28%)
Influenza	10 (8%)	8 (7%)
Upper Abdominal Pain	8 (7%)	6 (6%)
Nasopharyngitis	9 (7%)	4 (4%)
Somnolence	7 (6%)	7 (6%)
Vomiting	7 (6%)	3 (3%)
Dyspepsia	6 (5%)	4 (4%)

Insomnia	6 (5%)	11 (10%)
Diarrhoea	5 (4%)	11 (10%)
Dry Mouth	5 (4%)	14 (13%)
Fatigue	3 (2%)	11 (10%)
Ejaculation Disorder[1]	0	3 (10%)
Constipation	4 (3%)	9 (8%)
Back Pain	1 (<1%)	6 (6%)
1. Ejaculation disorder expressed as a percentage of male subjects		
Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]		
	Placebo (N = 123)	Paroxetine (N = 109)
Subjects with non-fatal SAEs, n (%)		
	n (%) [related]	n (%) [related]
Haemorrhoidal Haemorrhage	0	1 (<1%) [0]
Rash*	1 (<1%) [0]	0
Subjects with fatal SAEs, n (%)	0	0
*SAE of rash occurred during follow-up phase of study		

Conclusion: For the primary endpoint (change from baseline to Week 8 LOCF endpoint on the HAM-D total score), a greater reduction (i.e. improvement) from baseline to study endpoint was observed for paroxetine recipients compared to placebo. However, this difference was not statistically significant in the LOCF analysis (Week 8 LOCF: treatment difference -1.2; 95% C.I. -3.4, 1.0; p=0.282). Treatment emergent adverse events were reported by 86/109 (79%) paroxetine recipients and 82/123 (67%) placebo recipients. Common emergent adverse events (≥ 10%) reported by paroxetine recipients included headache, nausea, insomnia, diarrhoea, dry mouth, fatigue and ejaculation disorder. Common emergent adverse events (≥ 10%) reported by placebo recipients included nausea and headache. One subject receiving paroxetine and one subject receiving placebo reported an SAE. There were no fatal SAEs.

Publications:
No Publication

Date Updated: 24-May-2007