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Study No.: NKP103401
Title: A Randomized, Double-Blind, Parallel-Group, Placebo- Controlled Fixed Dose Study Comparing the Efficacy and Safety of New Chemical Entity (NCE)/Paroxetine combination or Paroxetine monotherapy to Placebo in Subjects with Social Anxiety Disorder (SAD).
Rationale: Paroxetine, a selective serotonin reuptake inhibitor (SSRI) has in some countries been approved for the treatment of Social Anxiety disorder (SAD). Potentially combining the SSRI and the NCEs mechanisms can result in a more efficacious and better tolerated antidepressant/anxiolytic drug. The purpose of the current study was to evaluate the efficacy, safety and tolerability of NCE/paroxetine combination in subjects with a primary diagnosis of SAD. This summary includes data for paroxetine and placebo groups only; information for the unmarketed NCE/paroxetine combination will be added, if and when the NCE is approved and marketed.
Phase: II
Study Period: 15 November 2004 - 19 September 2005.
Study Design: A 12-week randomised, multicentre, double-blind, placebo-controlled, fixed dose, parallel group study.
Centres: Sixteen centres in four countries: Denmark (six centres), Germany (four centres), South Africa (two centres) and Norway (four centres).
Indication: Social Anxiety Disorder (SAD).
Treatment: NCE/paroxetine combination, paroxetine monotherapy (7.5 mg/day, fixed dose) or placebo for a period of 12 weeks.
Objectives: To evaluate the anxiolytic efficacy of NCE/paroxetine combination compared to placebo in outpatients with SAD.
Primary Outcome/Efficacy Variable: Change from baseline in the clinician-administered Liebowitz Social Anxiety Scale (LSAS) total score at Week 12 last observation carried forward (LOCF). The primary comparison of interest was the NCE/paroxetine combination versus placebo.
Secondary Outcome/Efficacy Variable(s): • Change from baseline in the clinician-administered LSAS total score at Week 12 LOCF for the secondary comparison of interest (paroxetine monotherapy compared to placebo). • Change from baseline in the IVRS LSAS total score at Week 12 LOCF. • The proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression Global Improvement (CGI-I) item score at Week 12 LOCF. • Change from baseline in the Clinical Global Impression Severity of Illness (CGI-S) item score at Week 12 LOCF. • Change from baseline on the LSAS Fear subscale score at Week 12 LOCF. • Change from baseline on the LSAS Avoidance subscale score at Week 12 LOCF. • Change from baseline on the Social Avoidance and Distress Scale (SADS) total score at Week 12 LOCF. • Change from baseline on the Sheehan Disability Scale (SDS) total score at Week 12 LOCF. • Change from baseline on the SDS family life item at Week 12 LOCF. • Change from baseline on the SDS work item at Week 12 LOCF. • Change from baseline on the SDS social life item at Week 12 LOCF.
Statistical Methods: The primary comparison of interest was NCE/paroxetine combination versus placebo. The secondary comparison of interest was paroxetine monotherapy versus placebo. These treatment comparisons were considered for all primary and secondary endpoints. Since there was only one primary comparison (NCE/paroxetine combination versus placebo), no adjustment for multiplicity was performed. The primary population for efficacy and safety was the intent to treat (ITT) population. The (ITT) population was defined as consisting of all subjects who gave informed consent, were randomised, received at least one dose of double-blind medication and for whom at least one valid post-baseline evaluation was available. The primary analysis methodology for dealing with missing data was last observation carried forward (LOCF). All hypothesis tests were two-sided and comparisons of interest were performed at the 10% level of significance. *Continuous Endpoints*. The statistical model used was Analysis of Covariance and included terms for amalgamated centre, baseline score and treatment group, regardless of significance. *Binary Endpoint:* The proportion of responders who scored 1 or 2 (very much improved or much improved) on the CGI-I item was analysed using logistic regression. The model was fitted to include a term for amalgamated centre and treatment group.
Study Population: Male and female subjects, 18-65 years of age, with a primary diagnosis of Generalised Social

Anxiety Disorder/Social Phobia as defined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV, 300.23), diagnosed using psychiatric confirmation of diagnosis in conjunction with the Mini International Neuropsychiatric Interview (MINI), Clinician Rated version 5.0.
Subjects were excluded if they scored 1 or 2 on the CGI-I item at baseline; subjects with a score 15 or more on the Hamilton Depression (HAMD) Rating Scale 17 (HAMD-17) item at screening were also excluded. In addition, subjects were excluded if they had a history of myocardial infarction within one year prior to the screening visit, or had body dysmorphic disorder or had a history of schizophrenia, schizoaffective disorder, or a bipolar disorder.

Number of Subjects:	Placebo	Paroxetine	Total *
Planned, N	68	68	204
Randomised, N	65	68	201
N (ITT)	62	66	194
Completed, n (%)	43 (69.4)	43 (65.2)	130 (67.0)
Total Number Subjects Withdrawn, N (%)	19 (30.6)	23 (34.8)	64 (33.0)
Withdrawn due to Adverse Events n (%)	5 (8.1)	4 (6.1)	13 (6.7)
Withdrawn due to Lack of Efficacy n (%)	4 (6.5)	4 (6.1)	11 (5.7)
Withdrawn for other reasons n (%)	10 (16.1)	15 (22.7)	40 (20.6)
Demographics			
Females: Males	38:24	36:30	106:88
Mean Age, years (SD)	42.1 (11.84)	38.5 (10.58)	40.2 (11.40)
White, n (%)	62 (100.0)	65 (98.5)	190 (97.9)

* includes NCE/paroxetine combination

Primary Efficacy Results (for ITT): The primary efficacy results, NCE/paroxetine combination, will be presented if and when the NCE is approved and marketed.

Secondary Outcome Variable(s):

		Placebo N=62	Paroxetine N=66
Clinician-Administered LSAS Total Score	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	-	1.61 (-5.44, 8.65)
	Score at baseline Mean (SD)	76.5 (27.71)	83.2 (26.23)
	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -16.02 (3.10)	n=65 -14.42 (2.99)
IVRS LSAS Total Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=50 -19.41 (3.73)	n=50 -19.29 (3.63)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	-	0.12 (-8.41, 8.65)
Proportion of Responders on the CGI-I Scale	Responders, n/N (%)	18/62 (29.0)	17/65 (26.2)
	Treatment vs Placebo Adjusted Odds Ratio 90% CI for Odds Ratio	-	0.85 (0.43, 1.69)
CGI-S Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -0.59 (0.14)	n=65 -0.62 (0.14)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	-	-0.04 (-0.37, 0.29)
Clinician-Administered LSAS Fear Subscale Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -8.09 (1.57)	n=65 -6.90 (1.52)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	-	1.19 (-2.38, 4.75)
LSAS Avoidance Subscale Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -8.01 (1.61)	n=65 -7.48 (1.56)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	-	0.54 (-3.13, 4.21)
SADS Total Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -3.57 (0.93)	n=65 -4.26 (0.90)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	-	-0.70 (-2.81, 1.42)

SDS Total Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -3.58 (0.80)	n=65 -3.63 (0.77)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	- -	-0.05 (-1.87, 1.76)
SDS Family Life Item Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -0.64 (0.28)	n=65 -0.70 (0.27)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	- -	-0.06 (-0.68, 0.57)
SDS Work Item Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -1.12 (0.29)	n=65 -1.27 (0.28)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	- -	-0.15 (-0.80, 0.51)
SDS Social Life Item Score	Adjusted Change to Week 12 LOCF Adjusted Mean (SE)	n=62 -1.89 (0.32)	n=65 -1.69 (0.31)
	Treatment vs Placebo Adjusted Treatment Diff. at Week 12 LOCF 90% CI	- -	0.20 (-0.52, 0.92)

Adverse Event(s): An on therapy adverse event (AE) or serious adverse event (SAE) 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.

Adverse Events – On-Therapy Most Frequent 10 AEs in each group.	Placebo N=62	Paroxetine N=66
	n (%)	n (%)
Subjects with any AE(s), n(%)	38 (61.3)	39 (59.1)
Fatigue	8 (12.9)	8 (12.1)
Nausea	8 (12.9)	10 (15.2)
Headache	5 (8.1)	5 (7.6)
Dizziness	0	4 (6.1)
Nasopharyngitis	4 (6.5)	2 (3.0)
Diarrhoea	3 (4.8)	3 (4.5)
Dry Mouth	2 (3.2)	2 (3.0)
Influenza	1 (1.6)	2 (3.0)
Libido Decreased	3 (4.8)	4 (6.1)
Tremor	0	1 (1.5)
Anorgasmia	0	1 (1.5)
Hyperhidrosis	2 (3.2)	1 (1.5)
Cough	1 (1.6)	0
Erectile Dysfunction	0	2 (3.0)
Vertigo	1 (1.6)	0
Depression	1 (1.6)	3 (4.5)
Back Pain	0	2 (3.0)
Orgasm abnormal	0	2 (3.0)
Insomnia	5 (8.1)	1 (1.5)
Anorexia	2 (3.2)	0
Constipation	2 (3.2)	1 (1.5)
Decreased Appetite	2 (3.2)	0
Pain in Extremity	2 (3.2)	0
Vomiting	2 (3.2)	0

Serious Adverse Events On-Therapy n (%) [n considered by the investigator to be related to study medication]

	Placebo N=62	Paroxetine N=66
Subjects with non-fatal SAEs, n (%)	1 (1.6)	0
	n (%) [related]	n (%) [related]
Nasal septum deviation	1 (1.6) [0]	0 [0]
Subjects with fatal SAEs, n (%)	0	0

Conclusion:
There was no statistically significant difference in the change from baseline in clinician-administered LSAS total score at Week 12 LOCF, for paroxetine monotherapy (7.5 mg/day) versus placebo.

There were no statistically significant treatment differences between paroxetine monotherapy (7.5 mg/day) versus placebo, for the secondary efficacy endpoints presented here at Week 12 LOCF. The proportion of subjects with at least one AE during the treatment phase was similar between the placebo and paroxetine monotherapy (7.5 mg/day) groups.
Publications: None