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: CRH103390

Title : A 12 Week Flexible Dose Study of GW876008, Placebo and Active Control (Paroxetine) in the Treatment of Social Anxiety Disorder (SocAD)

Rationale: The primary purpose of this study was to evaluate GW876008 as a treatment for anxiety in subjects with generalized SocAD. Two doses of GW876008, placebo, and paroxetine (active control) were evaluated for safety, tolerability and efficacy.

Phase: II

Study Period: 08 Nov 2006 - 31 Aug 2007

Study Design: CRH103390 was a 12 week, multicenter, randomized, parallel, double-blind, active comparator and placebo controlled study in outpatients with a diagnosis of generalized SocAD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV). Two flexible dose ranges of GW876008 and a flexible dose range of paroxetine (20-30mg/day) were compared to placebo in four parallel treatment groups.

Centers: Multicenter study (12 centers in the US, 5 centers in Germany, 4 centers in Canada, and 3 centers each in Finland, Norway, Sweden, and South Africa).

Indication: Social Anxiety Disorder

Treatment: Subjects were randomized in a 2:2:2:1 ratio such that 81 subjects received GW876008 25-50mg/day, 83 received GW876008 100-125mg/day, 88 received placebo and 42 received paroxetine 20-30mg/day.

Objectives: To evaluate the anxiolytic efficacy of two dose ranges of NCE compared to placebo in outpatients with SocAD.

Statistical Methods: The population used in the key efficacy analyses was the intent to treat (ITT) population using the Mixed-Effects Model Repeated-Measure (MMRM) analysis for comparisons. This model included treatment, country, visit and treatment by visit as categorical effects and included Randomization Score and Randomization Score by Visit as continuous effects. An unstructured covariance structure was also used in the MMRM analysis. A logistic regression analysis was utilized to evaluate the proportion of Clinical Global Impression-Global Improvement (CGI-I) responders and the proportion of Liebowitz Social Anxiety Scale (LSAS) responders. The primary efficacy comparisons of interest were between each of two GW876008 dose groups and placebo for the change from randomization to Week 12 in the LSAS total score, LSAS Fear subscale score, LSAS Avoidance subscale score, and in the Social Avoidance and Distress Scale (SADS) total score. The comparisons between paroxetine and placebo were completed for all efficacy endpoints to evaluate the assay sensitivity of the study.

Study Population: Male and female subjects 18-64 years of age inclusive with a primary diagnosis of SocAD/Social Phobia diagnosed using criteria established in the DSM-IV (300.23) participated in the study. Subjects who scored 1 or 2 on the Clinical Global Impression-Global improvement (CGI-I) score item at the Randomization Visit, or who meet the DSM-IV criteria for Major Depressive Disorder or who scored ≥15 on the 17-Item Hamilton Rating Scale of Depression (HAMD-17) at the Screening Visit were excluded from participation.

Number of Subjects: ITT Population	**Placebo**	**GW876008 25-50 mg**	**GW876008 100-125 mg**	**Paroxetine 20-30mg**
Planned N	80	80	80	40
Dosed N	89	81	86	43
Completed n (%)	63 (72)	61 (75)	67 (81)	29 (69)
Total Number Subjects Withdrawn N (%)	25 (28)	20 (25)	16 (19)	13 (31)
Withdrawn due to Adverse Events n (%)	2 (2)	7 (9)	4 (5)	4 (10)
Withdrawn due to Lack of Efficacy n (%)	4 (5)	3 (4)	2 (2)	0 (0)
Withdrawn for Other Reasons n (%)	1 (1)	2 (2)	2 (2)	3 (7)

Demographics	Placebo	GW876008 25-50 mg	GW876008 100-125 mg	Paroxetine 20-30mg
N (ITT)	88	81	83	42
Females: Males	39:49	43:38	37:46	20:22
Mean Age in Years (SD)	37.5 (11.33)	36.8 (11.42)	38.4 (11.66)	36.7 (13.06)
Mean Weight in Kg (SD)	74.8 (16.51) [1]	82.9 (17.88)	81.7 (17.61)	74.5 (14.36)
Hispanic/Latino n (%)	7 (8)	5 (6)	2 (2)	2 (5)
Not Hispanic/Latino n (%)	81(92)	76 (94)	81 (98)	40 (95)
[1] n =87				
Efficacy Results (ITT population): This summary includes results for the primary and secondary efficacy variables utilizing the intent-to-treat (ITT) populations.				

Key Efficacy Endpoints (Change from Baseline)							
Visit WK	**Subscale test/ parameter**	**(N / n)**	**Adjusted Mean**	**Standard Error of Adjusted Mean**	**Difference vs. Placebo**	**90% CI for Treatment Difference**	**Two-Sided P-value for Treatment Difference**
LSAS Total score					-	-	-
Base line	Placebo	88/88	90.3	17.07	-	-	-
	GW876008 25-50 mg	81/81	90.2	18.57	-	-	-
	GW876008 100-125 mg	83/83	92.8	19.39	-	-	-
	Paroxetine	42/42	86.4	17.46	-	-	-
12	Placebo	88/65	-25.2	2.90	-	-	-
	GW876008 25-50 mg	81/65	-19.2	2.96	5.9	-0.9, 12.8	0.152
	GW876008 100-125 mg	83/69	-25.3	2.95	-0.1	-6.9, 6.7	0.979
	Paroxetine	42/31	-38.3	4.22	-13.1	-21.5, -4.6	0.011
LSAS Fear subscale							
Visit WK	**Subscale test/ parameter**	**(N / n)**	**Adjusted Mean**	**Standard Error of Adjusted Mean**	**Difference vs. Placebo**	**90% CI for Treatment Difference**	**Two-Sided P-value for Treatment Difference**
Base line	Placebo	88/88	46.5	8.51	-	-	-
	GW876008 25-50 mg	81/81	46.3	9.03	-	-	-
	GW876008 100-125 mg	83/83	47.4	9.55	-	-	-
	Paroxetine	42/42	44.1	8.55	-	-	-
12	Placebo	88/65	-12.5	1.48	-	-	-
	GW876008 25-50 mg	81/65	-9.8	1.51	2.7	-0.8, 6.1	0.210
	GW876008 100-125 mg	83/69	-12.2	1.50	0.2	-3.7, 3.3	0.916
	Paroxetine	42/31	-19.0	2.15	-6.5	-10.8, -2.2	0.013
LSAS Avoidance subscale							
Visit WK	**Subscale test/ parameter**	**(N / n)**	**Adjusted Mean**	**Standard Error of Adjusted Mean**	**Difference vs. Placebo**	**90% CI for Treatment Difference**	**Two-Sided P-value for Treatment Difference**
Base line	Placebo	88/88	43.9	9.22	-	-	-
	GW876008 25-50 mg	81/81	43.9	10.40	-	-	-
	GW876008 100-125 mg	83/83	45.4	10.37	-	-	-
	Paroxetine	42/42	42.3	9.82	-	-	-
12	Placebo	88/65	-12.8	1.48	-	-	-
	GW876008 25-50 mg	81/65	-9.5	1.50	3.3	-0.2, 6.8	0.119
	GW876008 100-125 mg	83/69	-13.0	1.50	-0.2	-3.7, 3.3	0.916
	Paroxetine	42/31	-19.3	2.14	-6.5	-10.8, -2.2	0.013
SADS Total Score							
Visit WK	**Subscale test/ parameter**	**(N / n)**	**Adjusted Mean**	**Standard Error of Adjusted Mean**	**Difference vs. Placebo**	**90% CI for Treatment Difference**	**Two-Sided P-value for Treatment Difference**
Base line	Placebo	88/85	23.9	4.34	-	-	-
	GW876008 25-50 mg	81/80	23.8	4.85	-	-	-
	GW876008 100-125 mg	83/83	23.7	4.98	-	-	-
	Paroxetine	42/42	24.4	3.56	-	-	-
12	Placebo	88/65	-5.8	0.85	-	-	-
	GW876008 25-50 mg	81/64	-4.5	0.87	1.4	-0.7, 3.4	0.270
	GW876008 100-125 mg	83/68	-4.0	0.87	1.8	-0.2, 3.8	0.142
	Paroxetine	42/31	-9.6	1.24	-3.8	-6.3, -1.3	0.013

Secondary outcome variables

CGI-S (Change from Baseline)

Visit WK	Subscale test/ parameter	(N / n)	Adjusted Mean	Standard Error of Adjusted Mean	Difference vs. Placebo	90% CI for Treatment Difference
Base line	Placebo	88/88	5.0	0.73	-	-
	GW876008 25-50 mg	81/81	5.0	0.69	-	-
	GW876008 100-125 mg	83/83	5.0	0.75	-	-
	Paroxetine	42/42	5.0	0.76	-	-
12	Placebo	88/65	-1.2	0.14	-	-
	GW876008 25-50 mg	81/65	-1.0	0.14	0.2	-0.1, 0.5
	GW876008 100-125 mg	83/69	-1.1	0.14	0.2	-0.2, 0.5
	Paroxetine	42/31	-2.1	0.20	-0.9	-1.3, -0.5

SDS total score (Change from Baseline)

Visit WK	Subscale test/ parameter	(N / n)	Adjusted Mean	Standard Error of Adjusted Mean	Difference vs. Placebo	90% CI for Treatment Difference
Base line	Placebo	88/82	18.6	5.47	-	-
	GW876008 25-50 mg	81/75	17.9	5.68	-	-
	GW876008 100-125 mg	83/74	18.6	6.73	-	-
	Paroxetine	42/41	17.3	5.34	-	-
12	Placebo	88/55	-5.7	0.75	-	-
	GW876008 25-50 mg	81/58	-3.8	0.77	1.9	0.2, 3.7
	GW876008 100-125 mg	83/58	-4.8	0.77	0.9	-0.9, 2.7
	Paroxetine	42/28	-8.0	1.06	-2.3	-4.5, -0.2

Visit WK	Subscale test/ parameter	(N / n)	Adjusted Mean	Standard Error of Adjusted Mean	Difference vs. Placebo	90% CI for Treatment Difference
LSEQ sub-scale score: Getting to Sleep						
12	Placebo	88/64	53.7	1.53	-	-
	GW876008 25-50 mg	81/66	51.4	1.52	-2.3	-5.9, 1.3
	GW876008 100-125 mg	83/66	54.2	1.42	0.5	-3.1, 4.1
	Paroxetine	42/31	59.2	2.20	5.5	1.1, 9.9
LSEQ sub-scale score: Quality of Sleep						
12	Placebo	88/64	52.9	1.93	-	-
	GW876008 25-50 mg	81/66	49.7	1.93	-3.1	-7.6, 1.4
	GW876008 100-125 mg	83/66	49.9	1.95	-3.0	-7.5, 1.6
	Paroxetine	42/31	54.1	2.78	1.2	-4.4, 6.8
LSEQ sub-scale score: Awakenings from Sleep						
12	Placebo	88/64	53.9	1.98	-	-
	GW876008 25-50 mg	81/66	51.3	1.97	-2.6	-7.2, 2.0
	GW876008 100-125 mg	83/66	50.4	1.98	-3.5	-8.1, 1.2
	Paroxetine	42/31	51.2	2.85	-2.7	-8.5, 3.0
LSEQ sub-scale score: Behaviour following Wakefulness						
12	Placebo	88/63	54.8	1.96	-	-
	GW876008 25-50 mg	81/66	48.9	1.95	-5.9	-10.4, -1.3
	GW876008 100-125 mg	83/66	48.3	1.96	-6.5	-11.1, -2.0
	Paroxetine	42/31	48.7	2.81	-6.1	-11.8, -0.5

CGI-I Responders

Visit	Subscale test/ parameter	(N / n)	Proportion of	Adjusted Odds	90% CI for Odds

WK			Responders n (%)	Ratio	Ratio
12	Placebo	88/88	32 (36%)	-	-
	GW876008 25-50 mg	81/81	20 (25%)	0.54	0.31, 0.96
	GW876008 100-125 mg	83/81	29 (36%)	0.96	0.56, 1.66
	Paroxetine	42/42	24 (57%)	2.43	1.27, 4.65

LSAS Responders

Visit WK	Subscale test/ parameter	(N / n)	Proportion of Responders n (%)	Adjusted Odds Ratio	90% CI for Odds Ratio
12	Placebo	88/88	14 (16%)	-	-
	GW876008 25-50 mg	81/81	12 (15%)	0.89	0.44, 1.83
	GW876008 100-125 mg	83/81	14 (17%)	1.12	0.56, 2.24
	Paroxetine	42/42	13 (31%)	2.38	1.13, 5.02

Safety results: Safety was assessed and AEs and SAEs recorded throughout the study from the Screening Visit until the Day 14 Follow-Up (end-of-study) Visit. Common AEs (>5% in any GW876008 group) in the Treatment Phase are listed below.

Adverse Events:	Placebo (N=88)	GW876008 25-50 mg (N=81)	GW876008 100-125 mg (N=83)	Paroxetine 20-30mg (N=42)
	n (%)	n (%)	n (%)	n (%)
Any Event	57 (65)	62 (77%)	56 (67%)	41 (98)
Headache	14 (16)	17 (21)	10 (12)	12 (29)
Fatigue	13 (15)	10 (12)	13 (16)	13 (31)
Dizziness	6 (7)	5 (6)	3 (4)	7 (17)
Nausea	7 (8)	4 (5)	7 (8)	13 (31)
Somnolence	2 (2)	6 (7)	0	7 (17)
Diarrhoea	6 (7)	4 (5)	5 (6)	4 (10)
Insomnia	3 (3)	4 (5)	6 (7)	1 (2)
Sleep disorder	2 (2)	1 (1)	6 (7)	3 (7)
Nasopharyngitis	6 (7)	9 (11)	5 (6)	7 (17)
Respiratory, thoracic & mediastinal disorders (any)	7 (8)	7 (9)	5 (6)	5 (12)
Musculoskeletal & connective tissue disorders (any)	7 (8)	5 (6)	5 (6)	4 (10)
Initial insomnia	0	5 (6)	0	1 (2)
Investigations (any)	6 (7)	3 (4)	7 (8)	4 (10)

Serious Adverse Events - On-Therapy
n (%)

	Placebo n (%)	GW876008 25-50 mg n (%)	GW876008 100-125 mg n (%)	Paroxetine n (%)
Subjects with non-fatal SAEs	0	0	0	0
Subjects with fatal SAEs	0	0	0	0

Clinical Laboratory Values

While there were sporadic instances of clinical laboratory values of potential clinical concern, there were no overall clinically significant laboratory findings (vital signs, clinical chemistries, hematologies, ECG reading, HPA hormones, HPG hormones, or serum Pepsinogen I levels). No subjects met the stopping criteria specified in the protocol for liver function tests.

Conclusions:

- There were no statistically significant differences at a two-sided level of 0.1 relative to placebo for either dose of GW876008 in any of the reported efficacy parameters.
- Statistically significant differences at a two-sided significant level of 0.1 were observed between paroxetine and placebo in all of the key efficacy parameters, indicating that the study had acceptable assay sensitivity.
- These results fail to support the hypothesis that GW876008 at doses up to 125 mg/day is beneficial in the treatment of SocAD.
- GW876008 was well-tolerated. The nature and frequency of AEs in the two doses of GW876008 were similar to that observed in the placebo group.
- There were no overall clinically significant laboratory findings.
- There were no deaths or non-fatal SAEs reported during the conduct of the study.

Publications: None