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.: SND103288
Title: A Ten-Week, Multicentre, Randomised, Double-Blind, Placebo-and Active-controlled, Parallel-Group, Flexible-Dose Study Evaluating the Efficacy, Safety and Tolerability of GSK372475, a New Chemical Entity (NCE), or Paroxetine Compared to Placebo in Adult Subjects Diagnosed with Major Depressive Disorder
Rationale: The primary purpose of this study was to evaluate the efficacy, safety, and tolerability of a NCE compared with placebo in the treatment of outpatient subjects with Major Depressive Disorder (MDD) with symptoms of decreased pleasure, interest and energy. This summary includes data for paroxetine and placebo groups. The NCE development was terminated in April 2009 but if the development re-start, results for the unmarketed NCE will be added, if and when the NCE is approved and marketed.
Phase: II
Study Period: 19 December 2006 to 24 June 2008
Study Design: A 10-week randomised, multicentre, double-blind, parallel-group, placebo- and active-controlled, flexible-dose study.
Centres: Thirty-five centres in 10 countries; 4 centres in Canada, 2 in Bulgaria, 5 in Croatia, 4 in France, 4 in Germany, 2 in Italy, 3 in Poland, 3 in Chile, 3 in Costa Rica, and 5 in India
Indication: Major Depressive Disorder (MDD)
Treatment: Subjects were randomised in a 1:1:1 ratio to 1 of 3 treatment regimens: NCE, paroxetine 20 mg/day (DL1) to 30 mg/day (DL2), or placebo. All subjects received DL1 for 4 weeks then progressed to DL2 if, in the investigator's judgement, the subject was not experiencing any troublesome adverse signs or symptoms and had not met response criteria.
Objectives: The objective of the study was to evaluate the antidepressant efficacy of the NCE compared with placebo in subjects diagnosed with MDD with symptoms of decreased pleasure, interest and energy.
Primary Outcome/Efficacy Variables: The key efficacy endpoints were change from Randomisation at Week 10 in Montgomery-Asberg Depression Rating Scale (MADRS) total score, the 6-item Bech scale from the Hamilton Depression Rating Scale – 17 item (HAMD-17) and the Inventory of Depressive Symptomatology – Clinician-Rated (IDS-CR) total score.
Secondary Outcome/Efficacy Variables: The secondary efficacy variables were: Change from Randomisation to Weeks 1, 2, 3, 4, 5, 6 and 8 in MADRS total score, IDS-CR total score and 6-item Bech scale extracted from the HAMD-17; Change from Randomisation to Weeks 1, 2, 3, 4, 5, 6, 8 and 10 in 16-item Quick Inventory of Depressive Symptomatology – Clinician Rating (QIDS-CR 16) total score, MADRS Item 2 score, HAMD-17 total score (protocol stated this was to be analysed at Week 10 but it was analysed at all weeks), Item 5 of the IDS-CR, Item 1 of the HAMD-17 and Clinical Global Impression – Severity of Illness (CGI-S); Change from Randomisation to Weeks 1, 4 and 10 in Inventory of Depressive Symptomatology – Self-Report (IDS-SR) total score, 16-item Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR 16) and Motivation and Energy Inventory (MEI) score; Change from Randomisation to Weeks 4 and 10 in Changes in Sexual Functioning Questionnaire; Percentage of responders at Weeks 1, 2, 3, 4, 5, 6, 8 and 10 in terms of MADRS, IDS, HAMD-17 and Clinical Global Impression – Global Improvement (CGI-I); Percentage of remitters at Weeks 1, 2, 3, 4, 5, 6, 8 and 10 in terms of MADRS, IDS and HAMD-17; Time to maintained antidepressant response in terms of MADRS total score, IDS-CR total score and HAMD-17 total score;

Time to maintained remission in terms of MADRS total score, IDS-CR total score and HAMD-17 total score;
Change from Randomisation to Week 10 and from Randomisation to Weeks 1, 2, 3, 4, 5, 6 and 8 in 5 item IDS-subscale;
Subject satisfaction with study medication Question score at Week 10.

Statistical Methods: The primary analyses comprised a Mixed Model Repeated Measures (MMRM) analysis to investigate the difference between NCE and Placebo and between paroxetine and placebo at the end of the study in the above 3 primary endpoints.
Secondary efficacy analyses comprised the same MMRM model fitted on the secondary endpoints, a logistic regression to investigate the percentage of responders/remitters and a Survival Analysis to investigate time to response/remission.
All analyses presented were performed on the Intent-to treat (ITT) population defined as all subjects who gave informed consent, were randomised, received at least 1 dose of double blind medication and for whom at least 1 post-randomisation assessment was available.

Study Population: Key inclusion criteria were:
Male and non-pregnant, non-lactating female subjects using adequate contraception between 18 to 64 of age (inclusive) with a diagnosis of major depressive episode (MDE) associated with MDD meeting Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) criteria whose current episode was of at least 12 weeks duration and less than 2 years and who exhibited symptoms of decreased pleasure, interest and energy as measured by the 5-item subscale of the IDS-SR. Subjects were also required to have an IDS-SR total score ≥25 at the Screening and Randomization Visits, a CGI-S score of ≥4 at the Randomization Visit and Signed informed consent
Key exclusion criteria were:
DSM IV Axis I Disorder other than MDD, secondary diagnosis of anxiety disorders are permissible
Any DSM IV Axis II disorder which could interfere with non-responsiveness to pharmacotherapy
Current diagnosis of Dementia
Unstable medical disorder, Risk of suicide, History of substance abuse or dependence

	Placebo	**Paroxetine**
Number of Subjects:		
Planned Evaluable Subjects, N	155	155
Randomised, N	160	172
Included in ITT population, N	156	166
Completed, n (% of ITT population)	115 (74)	128 (77)
Total Number Subjects Withdrawn, n (% of ITT population)	41 (26)	38 (23)
Withdrawn due to Adverse Events n (% of ITT population)	3 (2)	10 (6)
Withdrawn due to Lack of Efficacy n (% of ITT population)	6 (4)	4 (2)
Withdrawn for Other Reasons n (% of ITT population)	32 (21)	24 (15)
Demographics	**Placebo**	**Paroxetine**
N (ITT)	156	166

Females: Males	117:39	111:55
Mean Age, years (SD)	41.8 (10.89)	44.4 (10.90)
Not Hispanic/Latino, n (%)	126 (81)	133 (80)
Primary Efficacy Results (ITT population):		
	Placebo (N=156)	**Paroxetine (N=166)**
MADRS total score		
Baseline, mean (SD)	31.8 (5.51)	30.3 (5.45)
Change from Randomisation to Week 10 (Least Squares [LS] mean)	-16.09	-20.08
Difference versus placebo	-	-3.99
90% Confidence Interval	-	-5.75,-2.22
p-value	-	<0.001
6-item Bech scale from HAMD-17		
Baseline, mean (SD)	12.1 (2.24)	11.7 (2.21)
Change from Randomisation to Week 10 (LSmean)	-5.91	-7.68
Difference versus placebo	-	-1.77
90% Confidence Interval	-	-2.49,-1.05
p-value	-	<0.001
IDS-CR total score		
Baseline, mean (SD)	44.8 (8.64)	43.1 (8.32)
Change from Randomisation to Week 10 (LSmean)	-21.44	-26.55
Difference versus placebo	-	-5.12
90% Confidence Interval	-	-7.55,-2.68
p-value	-	0.001

Key Secondary Outcome Variable(s) (ITT population):

	Placebo (N=156)	Paroxetine (N=166)
IDS-SR total score (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-24.83	-31.06
Estimated difference versus placebo at week 10	-	-6.23
90% Confidence Interval	-	-9.21,-3.25
QIDS-SR 16 (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-9.58	-11.70
Estimated difference versus placebo at week 10	-	-2.12
90% Confidence Interval	-	-3.27,-0.97
MADRS Item 2 score (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-2.32	-2.82
Estimated difference versus placebo at week 10	-	-0.51
90% Confidence Interval	-	-0.77,-0.25
IDS-CR Item 5 score (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-1.3	-1.68
Estimated difference versus placebo at week 10	-	-0.37
90% Confidence Interval	-	-0.53,-0.22
HAMD-17 total score (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-10.89	-13.85
Estimated difference versus placebo at week 10	-	-2.96
90% Confidence Interval	-	-4.28,-1.64
Item 1 of HAMD-17 (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-1.64	-2.03

Estimated difference versus placebo at week 10	-	-0.39
90% Confidence Interval	-	-0.60,-0.19
CGI-S (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-1.8	-2.32
Estimated difference versus placebo at week 10	-	-0.52
90% Confidence Interval	-	-0.76,-0.28
MEI (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	28.14	34.37
Estimated difference versus placebo at week 10	-	6.22
90% Confidence Interval	-	1.97,10.48
5-item IDS-CR subscale (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-5.20	-6.35
Difference versus placebo	-	-1.15
90% Confidence Interval	-	-1.79,-0.50
5-item IDS-SR subscale (MMRM analysis)		
Change from Randomisation to Week 10 (LS mean)	-6.38	-8.15
Difference versus placebo	-	-1.77
90% Confidence Interval	-	-2.64,-0.90
Week 10 % responders	55	81
odds ratio (90% confidence interval)	-	3.48 (2.11,5.73)
Percentage of responders ((≥50% reduction from Randomisation in total score) at week 10:		

MADRS		
% responders	55	81
odds ratio (90% confidence interval)	-	3.48 (2.11, 5.23)
IDS-CR		
% responders	50	72
odds ratio (90% confidence interval)	-	3.27 (1.99,5.36)
HAMD-17		
% responders	51	72
odds ratio (90% confidence interval)	-	3.06 (1.86,5.02)
odds ratio (90% confidence interval)	-	2.97 (1.81,4.88)
Percentage of remitters		
MADRS (total score ≤11)		
Week 10 % remitters	45	68
odds ratio (90% confidence interval)	-	2.48 (1.52,4.05)
IDS-CR (total score ≤14)		
Week 10 % remitters	35	48
odds ratio (90% confidence interval)	-	1.50 (0.93,2.43)
HAMD-17 (total score ≤7)		
Week 10 % remitters	35	52
odds ratio (90% confidence interval)	-	1.83 (1.15,2.92)

Time to maintained antidepressant response until Week 10		
MADRS (≥50% reduction from Randomisation in total score)		
Hazard ratio (90% confidence interval)	-	2.49 (1.837, 3.375)
IDS-CR (≥50% reduction from Randomisation in total score)		
Hazard ratio (90% confidence interval)	-	2.25 (1.634,3.098)
HAMD-17 (≥50% reduction from Randomisation in total score)		
Hazard ratio (90% confidence interval)	-	2.25 (1.636,3.099)
Time to maintained remission until Week 10		
MADRS (total score ≤11) Hazard ratio (90% confidence interval)	-	1.98 (1.408,2.780)
IDS-CR (total score ≤14) Hazard ratio (90% confidence interval)	-	1.90 (1.268,2.833)
HAMD-17 (total score ≤7) Hazard ratio (90% confidence interval)	-	1.95 (1.307,2.905)
Subject satisfaction with study medication (at Week 10)		
Very dissatisfied, n (%)	12 (8)	10 (6)
Dissatisfied, n (%)	12 (8)	10 (6)
Slightly dissatisfied, n (%)	18 (13)	4 (2)
Neutral, n (%)	16 (11)	15 (9)
Slightly satisfied, n (%)	21 (15)	18 (11)
Satisfied, n (%)	34 (24)	56 (35)
Very satisfied, n (%)	31 (22)	49 (30)
% satisfied	45	64
Odds ratio (90% confidence interval)	-	2.45 (1.56,3.86)

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.

	Placebo (N=156)	**Paroxetine (N=166)**
Most Frequent Adverse Events – On-Therapy	**n (%)**	**n (%)**
Subjects with any AE(s), n(%)	91 (58)	104 (63)
Headache	36 (23)	26 (16)
Dry mouth	4 (3)	16 (10)
Nausea	12 (8)	26 (16)
Constipation	8 (5)	14 (8)
Diarrhoea	9 (6)	16 (10)
Insomnia	8 (5)	7 (4)
Somnolence	11 (7)	17 (10)
Dizziness	7 (4)	7 (4)
Nasopharyngitis	8 (5)	11 (7)
Back pain	6 (4)	8 (5)
Fatigue	8 (5)	8 (5)
Hyperhidrosis	5 (3)	7 (4)
Influenza	6 (4)	9 (5)
Sleep disorders	3 (2)	6 (4)

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

	Placebo (N=156)	NCE (N=171)	Paroxetine (N=166)
Subjects with non-fatal SAEs, n (%)	2 (1)	7 (4)	3 (2)
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Adjustment disorder with mixed disturbance of emotion and conduct	0	1 (<1) [0]	0
Depression	0	0	1 (<1) [0]
Major depression	0	1 (<1) [0]	0
Mania	0	1 (<1) [1]	0
Suicidal ideation	0	1 (<1) [0]	0
Influenza	0	1 (<1) [0]	0
Salpingitis	1 (<1) [0]	0	0
Haemorrhoidal haemorrhage	0	0	1 (<1) [0]
Chest pain	1 (<1) [0]	0	0
Cholelithiasis	0	1 (<1) [0]	0
Intentional overdose	0	0	1 (<1) [0]
Synovial cyst	0	1 (<1) [0]	0
Fatal Serious Adverse Events - On-Therapy **n (%) [n considered by the investigator to be related to study medication]**			
	Placebo (N=156)	**NCE (N=171)**	**Paroxetine (N=166)**
Subjects with fatal SAEs, n (%)	0	1 (<1)	0
	n (%) [related]	**n (%) [related]**	**n (%) [related]**
Completed suicide	0	1 (<1) [1]	0

Conclusion:
For each of the key efficacy endpoints (change from Randomisation at Week 10 in MADRS total score, the 6-item Bech scale from the HAMD-17 and the IDS-CR total score), paroxetine was statistically significantly superior compared with placebo. The results of the secondary endpoints were consistent with those of the primary endpoints. A total of 91/156 (58%) subjects in the placebo group, 113/171 (66%) subjects in the NCE group and 104/166 (63%) subjects in the paroxetine group had on-therapy AEs. The most frequently reported on-therapy AE was headache in the placebo and paroxetine groups and dry mouth in the NCE group. Two subjects in the placebo group, 7 subjects in the NCE group and 3 subjects in the paroxetine group had SAEs. There was 1 fatal SAE of completed suicide in the NCE group.

Publications: None.