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.

GSK Medicine: Emicerfont (GW876008); verucerfont (GSK561679)

Study Number: CRH108571

Title: Double-blind, randomized, placebo and Alprazolam-controlled three-period crossover incomplete block design study to compare putative anxiolytic-like fMRI activity of GW876008 and GSK561679 after single-dose administration in subjects with Social Anxiety Disorder (SAD)

Rationale: This study was designed to compare the functional magnetic resonance imaging (fMRI)brain activation maps and response to Public Speaking test after a single dose administration of either GW876008, GSK561679, placebo or alprazolam in subjects diagnosed with SAD.

Phase: I

Study Period: 27-Mar-2007 to 10-Jan-2008

Study Design: This was a double-blind, randomized, double-dummy, placebo-controlled 3 way crossover study. The study consisted of a screening period, 3 single treatment sessions a week apart (Weeks 1, 2, and 3) and a follow-up visit (Week 6). Within 21 days of the screening visit, eligible subjects with a primary diagnosis of SAD were randomized to a treatment sequence such that over the 3 treatment periods they each received alprazolam, placebo and either GW876008 or GSK561679. On each study day, subjects were administered a single dose of GW876008 or GSK561679 or placebo, followed 2 hours later by alprazolam or placebo. Subjects then underwent an fMRI procedure consisting of a series of activation and control tasks lasting approximately 1.5 h, after which they performed a Public Speaking test. On completion of the last treatment session, subjects completed a follow-up visit within 3 weeks.

Centres: The study was conducted at ten centres in Spain.

Indication: Social anxiety disorder

Treatment: Subjects were administered single oral doses of alprazolam (0.75 mg), placebo and either a single oral dose of GW876008 (200 mg) or GSK561679 (400 mg) across the 3 treatment periods, according to the randomization schedule. GW876008 and GSK561679 (or placebo) were administered, with a light snack, 3.5 ± 0.5 h prior to the fMRI procedure; alprazolam or placebo was administered 1.5 ± 0.5 h prior to the fMRI scan. This staggered dosing was to ensure adequate concentrations of each drug during the fMRI scan and Public Speaking task.

Objectives:

Primary

- To measure differences in fMRI blood oxygenation level dependent (BOLD) response in the amygdala or related limbic structures elicited by Matching Emotional Face Expression paradigm following single oral doses of GW876008 and GSK561679, respectively, vs. placebo (mood- congruent processing bias).
- To measure the differences in anxiety-related neuropsychological test scores elicited by a Public Speaking task following single oral doses of GW876008 and GSK561679, respectively, vs. placebo (stress response).

Secondary

- To measure changes in cortisol and adrenocorticotropic hormone (ACTH) levels following single doses of GW876008 and GSK561679, respectively, vs. placebo during the Public Speaking procedures.
- To measure changes in other indicators of stress response (i.e., neuropsychologic and autonomic) over time following single dose of GW876008 and GSK561679, respectively, vs. placebo during the whole testing day, and during the fMRI and Public Speaking procedures (profile test).
- To compare the potency of GW876008 vs. GSK561679 using pharmacokinetic/pharmacodynamic (PK/PD) models of the various endpoints (i.e.,imaging, neuropsychologic, autonomic, and endocrine) (profile test).
- To measure the effects of alprazolam 0.75 mg on the various endpoints (i.e.,imaging, neuropsychologic and autonomic) during fMRI and Public Speaking procedures and use these data as reference for the profiles of both the corticotrophin releasing factor 1 (CRF1) compounds (profile test).
- To measure changes in indicators of benzodiazepine side-effects produced by alprazolam vs. GW876008, GSK561679, respectively, or placebo during the whole testing day (profile test).
- To evaluate safety and tolerability of GW876008 and GSK561679.

Primary Outcome (Endpoints)/Efficacy

- fMRI BOLD response in the amygdala elicited by the Matching Emotional Face paradigm (mood-congruent processing bias) measured as % change of Signal activation between Face Condition and Shape Condition.
- Spielberger state-anxiety inventory (STAI-S) after the Public Speaking challenge (stress response)

Secondary Outcome (Endpoints)/Efficacy:

- From fMRI procedure:
    1. Indicators of physiological state during the fMRI session: Heart rate, respiratory rate, ventilation (pneumatic plethysmography), monitored during the whole procedure (control tests).
    2. fMRI BOLD response in the occipital and sensorimotor cortices produced by the finger opposition task and flashing checkerboard tests (control test)
    3. fMRI BOLD response in the insula (insulo-opercular region) elicited by the Matching Emotional Face paradigm (mood-congruent processing bias)
    4. fMRI BOLD response in other brain regions (e.g., thalamus, anterior cingulated or orbitofrontal cortex) elicited by the Matching Emotional Face paradigm (mood- congruent processing bias)
- Public Speaking test
    1. Visual analogue scale (VAS) measurements of distress (profile test)
    2. Plasma ACTH (profile tests).
    3. Plasma cortisol (profile test).
    4. Heart rate (profile tests).
- Benzodiazepine differentiation (side effects):
    1. Visual analog scale measurements of vigilance (profile test).
    2. Maddox wing test (blurred vision) (profile and safety).
    3. ARCI-PCAG questionnaire for sedation (safety).
    4. Pharmacokinetic measures and derived parameters if data permit (area under the plasma drug concentration curve from time 0 to last measurable concentration, maximum concentration, tmax).
- Pharmacokinetic/pharmacodynamic relationship between plasma levels of the various compounds and the primary and secondary pharmacodynamic endpoints
- Safety and tolerability were evaluated by AE monitoring, physical examination, electrocardiography (ECG), vital signs and laboratory parameters.

Statistical Methods: Sample size calculation was based on fMRI analysis: assuming a ratio effect/standard deviation (SD) within subject of at least 1.2, 32 subjects with 16 subjects treated both with GW876008 and placebo and 16 subjects treated both with GSK561679 and placebo would provide 90% power for each of the two primary comparisons of interest. This assumes a two-tailed test with alpha=5%..
The following populations were used:
Safety population: all subjects who received at least one dose of study drug
Pharmacodynamic population: all subjects of the Safety population who provided post-baseline data on pharmacodynamic parameters,
Pharmacodynamic fMRI BOLD population: those subjects in the Pharmacodynamic population who provided high-quality BOLD data with no movement artifacts,
Pharmacokinetic concentration population: all subjects for whom a pharmacokinetic sample was obtained and analysed.

All analyses were based on the actual treatment each subject received. Plasma concentration-time data were listed by treatment (GW876008 and GSK561679) and summarised using descriptive statistics by planned relative assessment time. Median values were plotted. STAI-S and VAS Distress Scores were analyzed using a mixed effect model including terms for treatment, period, time point, treatment x time point as fixed effects, and subject as a random effect. A similar model was utilized for the analysis of log-transformed ACTH and serum cortisol values. No formal statistical analysis was performed on safety data

Study Population: Key entry criteria were: men or women between 18 and 64 years of age, outpatient with a primary diagnosis of Social Anxiety Disorder diagnosed using psychiatric confirmation of diagnosis in conjunction with the mini

international neuropsychiatric interview (MINI). Liebowitz Social Anxiety Scale (LSAS) score of 50 or more.	
Number of Subjects:	**Overall study**
Planned, N	36
Randomized, N	35
Completed n (%) (Overall study)	35 (100)
Total Number Subjects Withdrawn (any reason) N (%)	0
Demographics (Safety Population)	**Overall study**
Age in years, Mean (Range)	25.6 (18–52)
Sex, n(%)	
Female:	23 (66)
Male:	12 (34)
Mean Body Mass Index in kg/m2) (SD)	23.18 (3.295)
Mean Height in cm (SD)	165.3 (11.30)
Mean Weight in kg (SD)	63.36 (9.218)
Race, n(%)	
American Indian or Alaskan Native	6 (17)
White – White/Caucasian/European Heritage	29 (83)

Primary Efficacy Results:

Differential Activation Pattern in Amygdala following Pharmacological Treatments vs. Placebo as determined by the 'Harsh Faces > Shapes' Contrast in the Emotional Face Matching Task

	Coordinates	**Cluster size (voxels)**	**T (maximum peak)***	**P value***
Alprazolam < Placebo (N=32)	L: -8 8 -16	L: 19 R: ns	L: 2.25	L: 0.013
GSK561679 < Placebo (N=16)	R: 26 -12 -12	L: ns R: 238	R: 2.94	R: 0.002
GW876008 < Placebo (N=16)	No suprathreshold results			

L=left; R=right; ns=non-significant; *=peak co-ordinates in the attenuated cluster

Lack of Biasing Effect of the Ventilation Profile as assessed as Covariate to the Main Dataset following Pharmacological Treatments in the 'Harsh Faces > Shapes' Contrast

Ventilation Covariate in Amygdala	**Coordinates**	**Cluster size (voxels)**	**T (maximum peak)***	**P value***
Alprazolam < Placebo (N=32)	L: -8 8 -14	L: 23 R: ns	L: 2.46	L: 0.008
GSK561679 < Placebo (N=16)	L: -260 -26 R: 30 -8 -20	L: ns R: 219	R: 3.01	R: 0.002
GW876008 < Placebo (N=16)	No supra-threshold results			

L=left; R=right; ns=non-significant; *=peak co-ordinates in the attenuated cluster

Results of Statistical Analysis of STAI-S Scores and Visual Analogue Distress Scale (Pharmacodynamic Population)

Time post dose	**Comparison**	**LS Means (Test Vs. Reference)**		**Difference (95% CI)**		**P value**	
		STAI-S	**VAS**	**STAI-S**	**VAS**	**STAI-S**	**VAS**

3.5–4 h	GW876008 -Placebo	40.8/40.2	NA	0.6 (-2.8, 3.9)	NA	0.735	NA
	GSK561679 - Placebo	40.0/40.2	NA	-0.2 (-3.5, 3.1)	NA	0.893	NA
	ALP – Placebo	38.3/40.2	NA	-1.9 (-4.6, 0.7)	NA	0.150	NA
	GW876008 –ALP	40.8/38.3	NA	2.5 (-0.8, 5.8)	NA	0.140	NA
	GSK561679 - ALP	40.0/38.3	NA	1.7 (-1.6, 5.0)	NA	0.302	NA
	GSK561679 – GW876008	40.0/40.8	NA	-0.8 (-4.8, 3.2)	NA	0.693	NA
4.5–5.3 h	GW876008 -Placebo	43.6/45.4	38.6/39.4	-1.8 (-6.0, 2.3)	-0.8 (-12.2, 10.6)	0.384	0.886
	GSK561679 - Placebo	44.7/45.4	48.4/39.4	-0.7 (-4.8, 3.4)	8.9 (-2.2, 20.1)	0.744	0.115
	ALP - Placebo	42.0/45.4	29.4/39.4	-3.4 (-6.7, -0.1)	-10.0 (-19.1, -0.9)	0.044	0.031
	GW876008 –ALP	43.6/42.0	38.6/29.4	1.6 (-2.6, 5.8)	9.2 (-2.2, 20.6)	0.453	0.113
	GSK561679 - ALP	44.7/42.0	48.4/29.4	2.7 (-1.3, 6.8)	19.0 (7.8, 30.2)	0.185	0.001
	GSK561679 – GW876008	44.7/43.6	48.4/38.6	1.2 (-3.7, 6.1)	9.8 (-3.6, 23.2)	0.638	0.150
5 h 20 min	ALP-Placebo	NA	21.1/33.2	NA	-12.1 (-20.3, -3.8)	NA	0.005
	GW876008 – ALP	NA	41.0/21.1	NA	19.8 (9.5, 30.2)	NA	<0.001
5 h 35 min	GW876008 -Placebo	44.6/42.1	45.6/34.1	2.5 (-1.2, 6.3)	11.5 (-1.3, 24.3)	0.187	0.079
	GSK561679 - Placebo	39.1/42.1	25.4/34.1	-2.9 (-6.6, 0.7)	-8.7 (-21.3, 3.8)	0.115	0.171
	ALP - Placebo	38.2/42.1	25.7/34.1	-3.9 (-6.9, -0.9)	-8.4 (-18.7, 1.8)	0.011	0.105
	GW876008 –ALP	44.6/38.2	45.6/25.7	6.4 (2.7, 10.2)	19.9 (7.1, 32.8)	0.001	0.003
	GSK561679 - ALP	39.1/38.2	25.4/25.7	1.0 (-2.7, 4.6)	-0.3 (-12.9, 12.3)	0.603	0.964
	GSK561679 – GW876008	39.1/44.6	25.4/45.6	-5.4 (-9.9, -1.0)	-20.2 (-35.2, -5.3)	0.017	0.009
5 h 43 min: after public speaking	GW876008 -Placebo	51.9/48.7	67.7/53.2	3.2 (-2.3, 8.6)	14.5 (-0.2, 29.1)	0.249	0.052
	GSK561679 - Placebo	49.1/48.7	51.1/53.2	0.3 (-5.0, 5.7)	-2.1 (-16.5, 12.2)	0.906	0.769
	ALP - Placebo	45.9/48.7	51.6/53.2	-2.8 (-7.2, 1.5)	-1.6 (-13.4, 10.1)	0.198	0.785
	GW876008 –ALP	51.9/45.9	67.7/51.6	6.0 (0.6, 11.5)	16.1 (1.5, 30.8)	0.031	0.032
	GSK561679 - ALP	49.1/45.9	51.1/51.6	3.2 (-2.2, 8.5)	-0.5 (-14.9, 13.9)	0.241	0.944

	GSK561679 – GW876008	49.1/51.9	51.1/67.7	-2.9 (-9.2, 3.5)	-16.6 (-33.6, 0.4)	0.371	0.055
6 h	GW876008 -Placebo	41.6/39.3	32.9/25.1	2.2 (-1.5, 5.9)	7.8 (-2.9, 18.4)	0.238	0.152
	GSK561679 - Placebo	40.2/39.3	27.9/25.1	0.9 (-2.8, 4.5)	2.8 (-7.6, 13.3)	0.631	0.589
	ALP - Placebo	37.2/39.3	19.1/25.1	-2.2 (-5.1, 0.8)	-6.0 (-14.5, 2.4)	0.150	0.160
	GW876008 –ALP	41.6/37.2	32.9/19.1	4.4 (0.7, 8.1)	13.8 (3.1, 24.5)	0.022	0.012
	GSK561679 - ALP	40.2/37.2	27.9/19.1	3.0 (-0.6, 6.7)	8.9 (-1.6, 19.4)	0.101	0.094
	GSK561679 – GW876008	40.2/41.6	27.9/32.9	-1.3 (-5.7, 3.1)	-4.9 (-17.5, 7.6)	0.548	0.439
6 h 20 min	GW876008 -Placebo	39.1/37.3	23.2/15.0	1.8 (-0.8, 4.4)	8.1(-0.1, 16.4)	0.176	0.054
	GSK561679 - Placebo	36.3/37.3	20.8/15.0	-1.0 (-3.6, 1.6)	5.8 (-2.3, 13.9)	0.442	0.157
	ALP - Placebo	34.9/37.3	12.6/15.0	-2.4 (-4.4, -0.3)	-2.4 (-8.9, 4.1)	0.025	0.460
	GW876008 –ALP	39.1/34.9	23.2/12.6	4.2 (1.5, 6.8)	10.5 (2.3, 18.8)	0.002	0.013
	GSK561679 - ALP	36.3/34.9	20.8/12.6	1.4 (-1.2, 3.9)	8.2 (0.1, 16.3)	0.298	0.046
	GSK561679 – GW876008	36.3/39.1	20.8/23.2	-2.8 (-6.0, 0.4)	-2.3 (-12.2, 7.6)	0.086	0.643
7 h	GW876008 -Placebo	36.4/35.0	18.3/11.8	1.4 (-1.1, 3.9)	6.6 (-0.4, 13.5)	0.268	0.064
	GSK561679 - Placebo	34.4/35.0	15.2/11.8	-0.5 (-3.0, 1.9)	3.5 (-3.4, 10.3)	0.653	0.315
	ALP - Placebo	35.0/35.0	9.8/11.8	-0.0 (-2.0, 1.9)	-1.9 (-7.4, 3.5)	0.963	0.480
	GW876008 –ALP	36.4/35.0	18.3/9.8	1.4 (-1.0, 3.9)	8.5 (1.5, 15.5)	0.253	0.017
	GSK561679 - ALP	34.4/35.0	15.2/9.8	-0.5 (-2.9, 1.9)	5.4 (-1.4, 12.2)	0.679	0.119
	GSK561679 – GW876008	34.4/36.4	15.2/18.3	-1.9 (-5.0, 1.1)	-3.1 (-11.6, 5.4)	0.209	0.470

ALP=alprazolam; CI = confidence interval; h = hour; LSMeans = least squares means; min = minute; NA = Not Applicable; STAI-S = Spielberger state-anxiety inventory; VAS = Visual analogue scale

Secondary Outcome Results:

Heart rate and respiratory rate were monitored during the whole procedure and the results are summarized as below (Safety Population).

		Placebo N=35		**GW876008 (200 mg) N=17**		**GSK561679 (400 mg) N=18**		**Alprazolam (0.75 mg) N=35**	
		n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Heart rate (BPM)	PRE-DOSE	35	66.1 (11.46)	17	70.1 (13.15)	18	63.5 (13.16)	35	66.4 (11.53)
	5 h 20 min	34	68.7 (12.87)	17	76.9 (17.30)	18	66.7 (10.93)	35	71.6 (12.19)
	5 h 43 min	35	90.6 (16.76)	17	97.9 (19.34)	18	86.2 (16.23)	35	94.3 (18.45)
	6 h	35	75.0 (12.76)	17	82.3 (15.17))	18	71.2 (12.03)	35	73.2 (13.03)
	6 h 20 min	35	71.0 (12.79)	17	75.8 (15.25)	18	67.6 (11.88)	35	71.5 (12.52)
Respiration rate (breaths/min)	PRE-DOSE	35	18.0 (2.70)	17	17.7 (3.82)	18	18.1 (3.27)	35	18.0 (3.85)
	5 h 20 min	34	17.7 (2.93)	17	19.4 (3.28)	18	17.3 (3.05)	35	18.3 (3.54)
	5 h 43 min	35	19.5 (5.16)	17	18.0(4.54)	18	24.4 (7.73)	35	21.8 (7.51)

	6 h	35	18.4 (5.28)	17	20.0 (6.64)	18	20.3 (7.95)	35	20.0 (7.73)
	6 h 20 min	35	16.3 (3.86)	17	17.5 (3.70)	18	19.9 (7.87)	35	19.2 (6.90)

BPM = beats per minute; h = hour; min = minute; SD = Standard Deviation

fMRI BOLD response in the occipital and sensorimotor cortices produced by the finger opposition task and flashing checkerboard tests (control test) was determined. The task produced a reliable activation profile in the expected brain region. No differences from placebo were observed with alprazolam, GSK561679 or GW876008. These results indicated the absence of a general vascular effect of the pharmacologic treatments and support the task-specific activation patterns

fMRI differential activation pattern in insula following pharmacological treatments in the 'harsh faces > shapes' contrast in the Emotional Face Matching task (Pharmacodynamic Population)

	Coordinates	Cluster size (voxels)	T (maximum peak)*	P value*
Alprazolam < Placebo (N=32)	L: -34 22 10	L: 101 R: ns	L: 2.42	L: 0.009
GSK561679 < Placebo (N=16)	R: 44 4 -14	L: ns R: 172	R: 2.24	R: 0.014
GW876008 > Placebo (N=16) [Amygdala]	R: 24 -10 -18	R: 140	R: 2.92	R: 0.002
GW876008 > Placebo (N=16) [Insula][1]	L: -42 24 4 L: -40 -10-16 R: 32 -26 -10 R: 40 -4 -14	L: 196 L: 213 R: 117 R: 83	L: 3.54 L: 2.65 R: 3.19 R: 2.11	L: <0.0005 L: 0.005 R: 0.001 R: 0.019

1. Statistics from the most representative clusters.

L=left; R=right; ns=non-significant; *=peak co-ordinates in the attenuated cluster.

fMRI Differential Activation Pattern in Other Brain Regions following Pharmacological Treatments in the 'Harsh Faces > Shapes' Contrast

	Coordinates	Cluster size (voxels)	T (maximum peak)*	P value*
Alprazolam < Placebo (N=32) [Thalamus]	ns			
Alprazolam > Placebo (N=32) [Orbitofrontal region]	L+R: -4 22 -2	L+R: 344	L+R: 3.75	L+R: <0.0005
GSK561679 < Placebo (N=16) [Thalamus]	L+R: -6 -18 14	L+R: 1863	L+R: 3.24	L+R: 0.001
GSK561679 > Placebo (N=16) [Orbitofrontal region]	L+R: -2 22 -2	L+R: 505	L+R: 3.34	L+R: 0.001
GW876008 < Placebo (N=16) [Thalamus]	No supra-threshold results			
GW876008 > Placebo (N=16) [Orbitofrontal region]	No supra-threshold results			

L=left; R=right; ns=non-significant; *=peak co-ordinates in the attenuated cluster.

Summary of Results of Statistical Analysis of Adrenocorticotropic Hormone (ACTH) (ng/mL) and Cortisol (nmol) Values (Pharmacodynamic Population)

		Geometric LS Means (Test Vs. Reference)		Ratio (95% CI)	
Time	**Comparison**	**ACTH**	**Cortisol**	**ACTH**	**Cortisol**
5 h 20 min	GW876008 -Placebo	12.1/13.2	285.4/258.9	0.92 (0.76, 1.10)	1.10 (0.83, 1.47)
	GSK561679 - Placebo	7.3/13.2	68.1/258.9	0.55 (0.46, 0.67)	0.26 (0.20, 0.35)
	ALP - Placebo	8.3/13.2	133.2/258.9	0.63 (0.55, 0.74)	0.51 (0.41, 0.65)
	GW876008 –ALP	12.1/8.3	285.4/133.2	1.45 (1.20, 1.74)	2.14 (1.61, 2.86)
	GSK561679 - ALP	7.3/8.3	68.1/133.2	0.87 (0.72, 1.05)	0.51 (0.38, 0.69)
	GSK561679 – GW876008	7.3/12.1	68.1/285.4	0.60 (0.48, 0.75)	0.24 (0.17, 0.34)
5 h 35 min	GW876008 -Placebo	13.0/13.3	277.9/253.3	0.98 (0.82, 1.18)	1.10 (0.82, 1.47)
	GSK561679 - Placebo	8.9/13.3	73.4/253.3	0.67 (0.55, 0.80)	0.29 (0.21, 0.39)
	ALP - Placebo	9.2/13.3	116.9/253.3	0.69 (0.60, 0.80)	0.46 (0.37, 0.58)
	GW876008 –ALP	13.0/9.2	277.9/116.9	1.42 (1.19, 1.70)	2.38 (1.78, 3.17)
	GSK561679 - ALP	8.9/9.2	73.4/116.9	0.97 (0.80, 1.17)	0.63 (0.47, 0.84)
	GSK561679 – GW876008	8.9/13.0	73.4/277.9	0.68 (0.54, 0.85)	0.26 (0.18, 0.38)
6 h	GW876008 -Placebo	13.8/13.4	355.8/284.3	1.03 (0.87, 1.22)	1.25 (0.95, 1.64)
	GSK561679 - Placebo	11.3/13.4	179.1/284.3	0.84 (0.71, 1.00)	0.63 (0.48, 0.83)
	ALP - Placebo	10.4/13.4	203.5/284.3	0.77 (0.68, 0.89)	0.72 (0.58, 0.89)
	GW876008 –ALP	13.8/10.4	355.8/203.5	1.33 (1.12, 1.57)	1.75 (1.33, 2.29)
	GSK561679 - ALP	11.3/10.4	179.1/203.5	1.08 (0.91, 1.29)	0.88 (0.67, 1.16)
	GSK561679 – GW876008	11.3/13.8	179.1/355.8	0.81 (0.66, 1.00)	0.50 (0.36, 0.71)
7 h	GW876008 -Placebo	10.6/10.7	229.4/203.2	0.99 (0.81, 1.21)	1.13 (0.86, 1.49)
	GSK561679 - Placebo	10.5/10.7	134.6/203.2	0.99 (0.80, 1.21)	0.66 (0.50, 0.88)
	ALP - Placebo	9.6/10.7	130.8/203.2	0.90 (0.76, 1.06)	0.64 (0.52, 0.80)
	GW876008 –ALP	10.6/9.6	229.4/130.8	1.10 (0.90, 1.35)	1.75 (1.33, 2.31)
	GSK561679 - ALP	10.5/9.6	134.6/130.8	1.10 (0.89, 1.35)	1.03 (0.78, 1.36)
	GSK561679 – GW876008	10.5/10.6	134.6/229.4	1.00 (0.78, 1.28)	0.59 (0.42, 0.83)

ACTH = Adrenocorticotropic hormone; ALP=alprazolam; CI = confidence interval; h = hour; LSMeans = least squares means; min = minute.

Summary Statistics of VAS vigilance scales by treatment and time (Pharmacodynamic Population)

Domain	**Time**	**Placebo N=35**	**GW876008 (200 mg) N=17**	**GSK561679 (400 mg) N=18**	**Alprazolam (0.75 mg) N=35**
Calm-Excited Mean (SD)	PRE-DOSE 1	43.5 (21.63)	48.3 (16.49)	42.6 (22.19)	35.6 (16.99)
	3.5 – 4 h	37.4 (19.47)	40.9 (21.76)	33.2 (18.06)	28.1 (18.14)
	8 h	28.4 (17.98)	30.5 (15.35)	32.9 (22.21)	24.1 (18.24)
Anxious-Tranquil Mean (SD)	PRE-DOSE 1	54.7 (21.88)	49.0 (21.18)	54.6 (28.88)	61.2 (21.40)
	3.5 – 4 h	60.6 (21.02)	55.1 (19.47)	60.0 (23.00)	67.2 (19.54)
	8 h	72.5 (18.90)	61.2 (24.04)	64.6(25.27)	77.5 (13.43)
Tense-Relaxed Mean (SD)	PRE-DOSE 1	55.2 (22.60)	48.9 (22.36)	56.0 (28.34)	59.5 (22.11)
	3.5 – 4 h	60.9 (20.99)	53.2 (19.92)	60.8 (21.45)	69.0 (19.58)
	8 h	74.9 (17.19)	74.0 (16.59)	70.1 (21.12)	77.1 (14.37)

Sleepy-Awake Mean (SD)	PRE-DOSE 1	57.7 (22.03)	56.8 (23.32)	53.1 (20.57)	58.0 (22.56)
	3.5 – 4 h	56.5 (23.12)	59.4 (20.67)	58.3 (24.58)	43.6 (19.56)
	8 h	63.5 (22.57)	64.7 (17.15)	65.7 (19.00)	51.4 (22.81)
Alert-Drowsy Mean (SD)	PRE-DOSE 1	46.2 (20.36)	52.3 (16.51)	51.0 (16.66)	45.9 (21.63)
	3.5 – 4 h	45.4 (17.88)	40.6 (18.99)	43.8 (22.44)	55.0 (19.01)
	8 h	39.6 (18.52)	43.1 (13.07)	40.7 (18.60)	48.5 (20.56)

VAS = Visual analog scale; h = hour; min = minute; SD = Standard deviation

Summary of Plasma GW876008 and GSK561679 Pharmacokinetic Concentration- Time Data (ng/mL) (Pharmacokinetic Population)

	Planned Relative Time (h)	N	Mean	Standard Deviation	Median	Minimum	Maximum
GW876008 (ng/mL)	1	2	875.38	112.03	875.38	796.16	954.60
	2	17	1024.49	620.83	914.79	130.47	1957.11
	4–5	17	1161.78	474.52	1125.76	271.01	1868.46
	8	17	820.02	335.58	702.23	169.46	1333.14
GSK561679 (ng/mL)	1	4	703.39	414.28	721.97	282.36	1087.25
	2	17	1006.62	517.20	1147.89	237.01	2212.77
	4–5	17	786.72	286.66	781.74	193.99	1232.12
	8	17	232.68	97.13	245.02	60.04	400.11

h = hour

The pharmacokinetic/pharmacodynamic relationship between plasma levels of the various compounds was not analyzed

Safety Results: All 35 subjects reported at least one AE during the study and a total of 167 AEs were reported. Most AEs were judged to be either of mild or moderate intensity by the Investigator. One subject experienced dysmenorrhoea of severe intensity following a single dose of GW876008 200 mg, which was unrelated to the investigational product.

The Maddox Wing and ARCI-PCAG tests were used to assess the possible presence of sedation and other AEs during the clinical phase and were required to be negative before subject discharge from the unit.

Electrocardiography, vital signs and laboratory parameters were not reported as AEs following any active treatments.

A summary of AEs occurring in at least two subjects after any treatment are presented in the table below.

Adverse Events:	**Placebo N=35 n(%)**	**GW876008 N=17 n(%)**	**GSK561679 N=18 n(%)**	**Alprazolam N=35 n(%)**
Subjects with any AE(s), n(%)	24 (69)	11 (65)	11 (61)	33 (94)
Somnolence	10 (29)	3 (18)	5 (28)	28 (80)
Headache	9 (26)	5 (29)	1 (6)	5 (14)
Dizziness	3 (9)	1 (6)	1 (6)	5 (14)
Fatigue	3 (9)	0	0	2 (6)
Dysmenorrhoea	1 (3)	3 (18)	0	4 (11)
Ataxia	1 (3)	0	0	6 (17)
Nasopharyngitis	0	0	1 (6)	3 (9)

Serious Adverse Events - On-Therapy

No non-fatal or fatal SAEs were reported during the study. No subjects prematurely discontinued any investigational product and/or the study.

Conclusion: GSK561679 and alprazolam produced attenuation of the fMRI BOLD response in the amygdala elicited by the Matching Emotional Face paradigm. Conversely, activation was seen with GW876008 suggesting functional differences between the two CRF1 antagonists. GSK561679 and alprazolam produced a trend for attenuation of the STAI-S vs. placebo while GW876008 produced a trend for worsening. Visual analogue scale measurements of distress showed changes similar to the STAI-S, supporting a trend for distress-reducing effects of GSK561679 and alprazolam, and distress-enhancing effect of GW876008. The large variability vs. sample size prevented proper signal detection.

Control tasks indicated minimal interference produced by the respiratory rate changes (as assessed by pneumatic plethysmography) with the BOLD signals produced by the Emotional Face Matching task.

No global vascular effects produced by exposure to the compounds were observed in the occipital and sensorimotor cortices produced by the finger opposition task and flashing checkerboard tests.

GSK561679 and alprazolam produced significant attenuation of the fMRI BOLD response in the insula elicited by the Matching Emotional Face paradigm while GW876008 produced significant activation.

fMRI BOLD response in other brain regions (i.e., thalamus and orbitrofrontal cortex) elicited by the Matching Emotional Face paradigm was explored. In the thalamus, GSK561679 produced significant attenuation of the fMRI BOLD response while alprazolam and GW876008 did not show any effect, suggesting extended attenuating effects of the 'anxiety brain circuit'. In orbitofrontal cortex, GSK561679 strongly enhanced the fMRI BOLD signal with a clear extension to area B25, suggesting possible effects on neurobiological substrates of depression. Alprazolam had a more restricted activation effect while GW876008 was not active.

Plasma ACTH was reduced by GSK561679 and alprazolam. Plasma cortisol profiles offered a clearer picture by showing a difference between GSK561679 and alprazolam vs. placebo and GW876008, the former showing lower values throughout the study. This effect is in line with the anxiolytic properties of GSK561679 and alprazolam, suggesting anti-stress effects.

No SAE was reported and all AEs were of mild or moderate intensity. Somnolence and headache were the most frequently reported AEs, mainly in the alprazolam and placebo treatments. Sedation and mild ataxia were observed after dosing with alprazolam. No relevant treatment- related vital sign changes were reported with any treatment.