Synopsis

Identifier: HM2008/00076/00 **Study Number:** CRI103143

Title: A Phase IIa, single-centre, randomised, placebo-controlled, double-blind, three-period crossover exploratory study investigating the effects on gut autonomic responses of single administration of either 20 mg or 200 mg GW876008, a corticotrophin-releasing factor 1(CRF1) antagonist, to adult patients with irritable bowel syndrome(IBS).

Investigator: [redacted] BSc, MD, FRCP

Study centre: This study was conducted at one centre: [redacted] United Kingdom [redacted]

Publication: None at the time of this report.

Study period:

Initiation Date: 08 DEC 2006

Termination Date: 15 OCT 2007

Phase of development: IIa

Objectives:

Primary

The primary objective of this Phase IIa exploratory study was to test the hypothesis that acute therapeutic effects of GW876008 in IBS patients would reverse stress-induced visceral hypersensitivity as evidenced by changes in rectal mucosal blood flow (RMBF) and/or rectal thresholds for perception and pain; thus suggesting a potential utility in the treatment of IBS.

Secondary

- Assess the safety and tolerability of GW876008 in adults with IBS.
- Assess the effects of GW876008 on thresholds for rectal pain sensitivity in adults with IBS.

Methodology:

The purpose of this study was to evaluate the acute therapeutic effects of GW876008 in IBS patients by assessing the reversal of stress-induced visceral hypersensitivity. There is the continuing need for the development of more effective therapeutics for IBS. Acute physiological and psychological stress produces an exacerbation of IBS symptoms. Pre-clinical data supported the hypothesis that administration of the CRF1- receptor antagonist GW876008 might be a clinically important therapy for IBS. Data also

suggested that visceral hypersensitivity testing with acute physiological and psychological stressors was reproducible and sensitive to clinically meaningful therapeutic intervention and could be used as a method for screening new IBS therapies. Clinical pharmacokinetic and safety data supported single dose exposures of this compound to male and female subjects.

This was a single-centre, randomised, double-blind, placebo-controlled, three-period crossover study of two single doses of GW876008 versus placebo.

The Screening assessments were conducted over two visits and were completed within 7-14 days before the first study day. The study consisted of 3 test periods, each separated by approximately one month, followed by a 7-14 day Follow-up period. For each study visit, the subjects attended the research facility for approximately 3 hours (h) at approximately the same time of the morning on each occasion. On arrival, the subjects were asked to complete the Hospital Anxiety and Depression (HAD) questionnaire.

Subjects were randomised to receive a single dose of study medication, which was either placebo, 20 mg or 200 mg of GW876008, in each period (see Treatment administration below). Each subject was also randomised to the order of the stress type administered, carried out in a 1:1 ratio.

Sequence	Stress 1	Stress 2
1	Physiological	Psychological
2	Psychological	Physiological

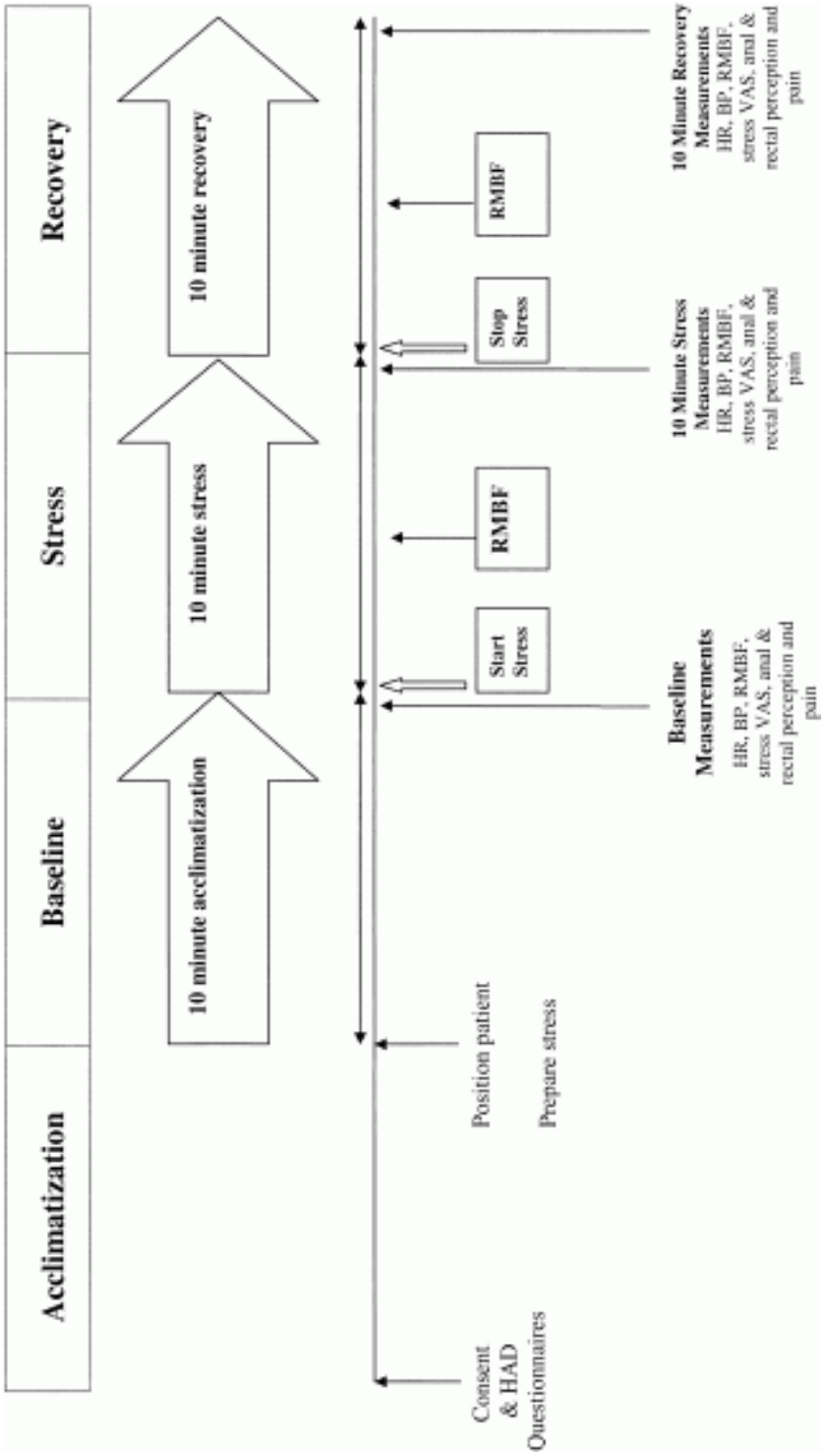
Physiological stress and the psychological stress was evoked using the well-validated technique of the cold water pressor test [O'Brien, 1987] and the dichotomous listening test [Emmanuel, 2000; Rao, 1998], respectively.

Blood samples were to be collected at 4 h after drug administration and, if a subject experiences a severe or serious adverse event (SAE), blood samples were also to be collected at 6 h and 24 h post dose.

Each subject's participation in the study was approximately 14 weeks (from Screening to Follow-up). A Time and Events table is provided as Attachment 1.

The following figure shows a schematic diagram of study day assessments

Schematic Diagram of Study Day Assessments



Number of subjects:

Subject Disposition and Demographics:

Number of Subjects	Treatment Sequence					Total
	B/C/A	C/A/B	B/A/C	A/C/B	C/B/A	
Number of subjects planned, N:	-	-	-	-	-	36
Number of subjects randomised, N:	2	2	2	1	2	9[1]
Number of subjects included in All subjects (safety) population, n (%):	2 (100)	2 (100)	2 (100)	1 (100)	2 (100)	9 (100)
Number of subjects included in PK population, n (%):	2 (100)	2 (100)	2 (100)	1 (100)	2 (100)	9 (100)
Number of subjects completed, n (%):	2 (100)	2 (100)	1 (50)	1 (100)	2 (100)	8 (89)
Number of subjects withdrawn (any reason), n (%):	0	0	1 (50)	0	0	1 (11)
Number of subjects withdrawn for SAE, n (%):	0	0	1 (50)	0	0	1 (11)
Reasons for subject withdrawal, n (%):						
Adverse events	0	0	1 (50)	0	0	1 (11)
Demographics	Total (N= 9)					
Age in Years, Mean (Range)	36.1 (20- 51)					
Sex, n (%)						
Female:	8 (89)					
Male:	1 (11)					
BMI (kg/m^2), Mean (Range)	24.63 (20-34)					
Height (cm), Mean (Range)	163.2 (153-171)					
Weight (kg), Mean (Range)	65.70 (55.7-96.0)					
Ethnicity, n (%)						
Hispanic or Latino:	0					
Not Hispanic or Latino:	9 (100)					
Race, n (%)						
White	9 (100)					

Data Source: Table 9.1, Table 9.2, Table 9.3 and Table 9.4
BMI= Body mass index
A= Placebo, B= 20 mg GW876008, C= 200 mg GW876008
1. Due to slow recruitment, the target sample size was reduced (based on sensitivity analysis) and only 9 subjects were included in the study.

Diagnosis and main criteria for inclusion:

Adult males and females between 18 and 65 years of age, inclusive with irritable bowel syndrome (clinical diagnosis guided by Rome II criteria) and with diarrhoea >70% of the days during Screening period (minimum of 14 days) were considered for the study. Subjects were non-smokers (abstinence from smoking for at least 6 months before the start of the study) with body weight ≥50 kg for men and ≥45 kg for women and body mass index (BMI) within the range 18.5 and 29.9 kg/m^2 inclusive.

Subjects who had taken any medication for the treatment of IBS within 6 months or corticosteroids within 3 months prior to Screening and the subjects who were taking Non steroidal anti-inflammatory drugs on a regular basis or within 48 hours of a study day were excluded from the study. Subjects with <10% reduction in RMBF following psychological stress at Screening visit 2 and the subjects with a HAD score of 7 or more were excluded from the study. All subjects provided written informed consent to participate in the study.

Listing of subjects with inclusion and exclusion criteria deviations is summarised in Table 10.12.

[redacted] These subjects were permitted to enter the trial following discussion with the Sponsor.

[redacted] The subject was permitted to enter the trial by the Investigator. This subject was a protocol deviation due to the concomitant medication of citalopram.

Treatment administration:

Each subject was randomised to receive one of the 6 treatment sequences outlined in the following table. The randomisation was carried out using a 1:1:1:1:1:1 ratio.

Treatment Sequence

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	B	C	A
3	C	A	B
4	B	A	C
5	A	C	B
6	C	B	A

Where the regimens are:

A: Placebo

B: 20 mg GW876008 (2 x 10 mg tablet)

C: 200 mg GW876008 (2 x 100 mg tablet).

At each dosing session subjects received a combination of active and placebo tablets in order to achieve the double-blind design. The details of each dosing regimen are summarised in the following table:

Summary of Treatment Administration

Regimen	N	Description	Dose Administered	Route	Batch Number
A	9	Single dose of Placebo	Two Placebo tablets to match 10 mg tablets + 2 Placebo tablets to match 100 mg tablets	Oral	041044651 (Placebo to match 10 mg tablets). 041044652 (Placebo to match 100 mg tablets)
B	9	Single dose of 20mg GW876008	Two tablets of 10 mg GW876008 + 2 Placebo tablets to match 100 mg tablets	Oral	041044671 (10 mg GW876008)
C	8	Single dose of 200mg GW876008	Two tablets of 100 mg GW876008 + 2 Placebo tablets to match 10 mg tablets	Oral	041044712 (100 mg GW876008)

Criteria for evaluation:

The primary endpoints were:

- The change from baseline in Laser Doppler regional RMBF measured in response to physiological stress (cold water pressor test).
- The change from baseline in Laser Doppler regional RMBF measured in response to psychological stress (dichotomous listening test).

The secondary endpoints were:

- Safety as assessed by adverse event (AE) reporting and laboratory analytes.
- Subject perceived stress as assessed by a visual analogue scale (VAS).
- Systemic autonomic nervous system response as assessed by blood pressure and heart rate.
- Visceral (rectal) electro sensitivity as assessed by subject reported threshold for perception of an electrical stimulus and reported threshold for pain.
- Baseline changes in RMBF at 90 minutes post dose.

Statistical methods:

Sample size consideration and justification

The estimates of the within-subject standard deviation for Laser Doppler RMBF measured in response to both physiologic and psychological stress were 13.7% and 10.3%, respectively. For this sample size calculation the physiologic stress variability was used, due to the greater variability observed. The calculation was based on a two-tailed procedure with power of at least 90%, to detect a difference of 20% in the Laser Doppler RMBF measured in response to both physiologic and psychological stress, should it exist with a Type I error rate of 5%. No adjustment was made for multiple comparisons.

A sensitivity analysis was undertaken on the within-subject variability estimate above to account for sampling error. The 95th percentile for the within-subject coefficient of variation, for physical stress, was 18.2%. Using this estimated within-subject variability, it was estimated that 36 patients would provide at least 90% power to detect a difference of 20% in the Laser Doppler RMBF measured in response to both physiologic and psychological stress, should it exist.

Due to this study terminating early due to slow recruitment, an ad-hoc sensitivity analysis was conducted to assess the power available to detect various RMBF treatment differences based on sample sizes of 5, 6, 8, 10 and 12 subjects (see Table Sensitivity Analysis below). Based on these calculations, the target sample size was reduced to 8 subjects.

Sensitivity Analysis

	RMBF Treatment Difference				
N	20%	30%	40%	50%	60%
5	23%	44%	65%	82%	92%
6	31%	58%	81%	94%	99%
8	46%	78%	95%	99%	99%
10	58%	90%	99%	99%	99%
12	68%	95%	99%	99%	99%

Final analysis

The primary analysis was to test the hypothesis that there was no treatment effect of either GW876008 20 mg or 200 mg on the change from baseline in Laser Doppler RMBF measured in response to both physiologic and psychological stress, compared to placebo. Point estimates and 95% confidence intervals (CI) were derived for the comparison of GW876008 20 mg with placebo and GW876008 200 mg with placebo.

The 95% CI provided a range of plausible values for the true difference between the regimens.

No formal statistical analysis of safety data was planned.

The percentage change from baseline in Laser Doppler RMBF measured in response to both physiologic and psychological stress was analysed using mixed model analysis of covariance (ANCOVA), fitting a model with regimen, time, stress order and period as fixed effects and subject as a random effect. Baseline (pre-dose) stress was fitted as a covariate. The residual variance from the model was used to calculate 95% CI for the differences in Least-squares (LS) means between GW876008 20 mg and placebo, and GW876008 200 mg and placebo. Distributional assumptions underlying this analysis were assessed by inspection of residual plots. No adjustment for multiple comparisons has been made

Change from planned analysis

The study was terminated earlier due to slow recruitment.

There were deviations from the randomisation schedule for stress type ordering: the order of stress type was not followed for all subjects (the listing of subject deviation is given in Table 11.24).

The final model ANCOVA did not include sequence effect because of the small number of subjects randomised to each sequence.

Based on the results from Murray et al [Murray, 2004], the rectal sensitization discriminated between IBS patients and healthy controls. During psychological stress, rectal threshold perception levels decreased by 19.4% ± 6% versus 8% ± 6% (IBS versus controls; probability(p) <0.01) and rectal pain thresholds decreased significantly more in patients with IBS: by 28.4% ± 4% versus 3.4% ± 3.8% (IBS versus controls; p<0.001). Hence during this study, the perception of electrical stimulus and of pain were also analysed analogously to RMBF measurements.

The correlation between VAS and RMBF at baseline as well as between HAD scores at start of assessment day and RMBF at baseline were explored.

Baseline values of VAS score were compared across the three treatments. The model used included regimen, stress order and period as fixed effects and subject as a random effect.

Full details of the statistical methods are provided in the Report and Analysis Plan (Attachment 2).

Blood samples were to be analysed only if a severe or serious adverse event occurred. [redacted]
The concentrations were summarised using three categories based on the time of sample collection relative to the time of administration of study treatment: (i) sample collected between 3.5 h and 4.5 h post-dose; (ii) sample collected between 6.25 h and 7.5 h post-dose; or (iii) sample collected outside these ranges. Concentrations were also plotted against the following pharmacodynamic endpoints: RBMF and rectal perception during physical and psychological stress using the first two sampling categories. The response was expressed as a percent change from baseline at 10 minutes (min) after stress.

Summary:

Pharmacodynamics:

Rectal mucosal blood flow.

RMBF data and the change from baseline in the measurements are summarised in Table 11.1, Table 11.2 and Table 11.3. The subject plot of the RMBF measurements and of the change from baseline (both on original scale and as % of the baseline value) over time, separately by treatment and stress typology, are given in Figure 11.1, Figure 11.2 and Figure 11.3, respectively. Regarding the assessment of RMBF, no major deviation from scheduled time was observed.

The analysis of variance (ANOVA) results for RMBF % change from baseline is given in Table 11.9 and summarised in Table 11.10 and Table 11.11. The plots of the LS means estimate with 95% CI for the % change from baseline in RMBF measurements in response to physiological and psychological stress are given in Figure 11.6 and Figure 11.7 respectively.

There was no evidence of deviation from normality of the data.

For both RMBF measurements in response to physiological and psychological stress:

- There was evidence of a time effect $p<0.001$; no evidence of time by treatment interactions or of overall treatment difference ($p>0.1$).
- There was no evidence of difference between the active treatment and placebo at any time point analysed.
- No effect of stress sequence or period effect.
- There was evidence that the baseline values were significant for the psychological stress.

The LS means estimates of the differences between active treatments and placebo in % change from baseline are given in the following table, with a positive difference between treatment and placebo indicating a quicker recovery for the treatment group.

RMBF LS means Estimate of Difference in Percent Change from Baseline

Stress type	Test - Reference	Planned relative time	Test LS mean	Reference LS mean	LS means Estimate of difference (95% Confidence Interval)	P value
PHY	C-A	Stress 5 minutes(min)	-22.11	-23.57	1.47 (-22.82, 25.75)	0.902
		Stress 10 min	-17.44	-32.35	14.91 (-6.20, 36.01)	0.157
		Recovery 5 min	0.52	-7.10	7.62 (-15.58, 30.82)	0.505
		Recovery 10 min	9.05	-1.95	11.00 (-11.79, 33.79)	0.329
	B-A	Stress 5 min	-22.93	-23.57	0.64 (-20.67, 21.96)	0.951
		Stress 10 min	-25.52	-32.35	6.83 (-10.90, 24.55)	0.432
		Recovery 5 min	-14.18	-7.10	-7.08 (-27.19, 13.03)	0.474
		Recovery 10 min	-12.40	-1.95	-10.46 (-30.11, 9.20)	0.282
PSY	C-A	Stress 5 min	-22.48	-22.26	-0.22 (-24.97, 24.53)	0.985
		Stress 10 min	-24.83	-21.97	-2.87 (-28.14, 22.41)	0.811
		Recovery 5 min	-6.10	-7.00	0.90 (-32.91, 34.71)	0.957
		Recovery 10 min	6.86	-4.88	11.73 (-10.84, 34.31)	0.279
	B-A	Stress 5 min	-13.28	-22.26	8.98 (-12.68, 30.64)	0.394
		Stress 10 min	-13.11	-21.97	8.85 (-13.32, 31.03)	0.404
		Recovery 5 min	5.00	-7.00	12.00 (-19.38, 43.39)	0.435
		Recovery 10 min	11.11	-4.88	15.98 (-3.09, 35.06)	0.093

Data Source: Table 11.11.
PHY: physiological, PSY: psychological

Visual analogue score.

VAS questionnaire results are summarised in Table 11.4 and Table 11.5. The subject plot of the VAS score and of the change from baseline in VAS score over time, separately by treatment and stress typology, are given in Figure 11.4 and Figure 11.5 respectively. [redacted]

The correlation plots between VAS score and RMBF at baseline are given in Figure 11.16 and the correlation values are given in Table 11.18. No significant correlations were observed across all treatment groups or within treatment with the exception of treatment GW876008 200 mg but caution should be taken in interpreting these results given the small number of subjects.

The results of analysis of VAS baseline values by stress type are reported in Table 11.23 There was no evidence of difference in baseline VAS score between the three treatment groups ($p>0.1$).

Threshold for perception of electrical stimulus and for pain

The reported threshold for perception of electrical stimulus and for pain is summarised in Table 11.6 and Table 11.7, respectively and the % change from baseline pain threshold and baseline electrical sensory threshold is summarised in Table 11.21 and Table 11.22, respectively. The subject plots of the raw data and of the % change from baseline are given in Figure 11.8, Figure 11.9, Figure 11.10 and Figure 11.11.

The ANOVA results for perception of pain % change from baseline is given in Table 11.12 and summarised in Table 11.13 and Table 11.14. The plots of the LS means estimate with 95% CI for the % change from baseline in perception of pain in response to physiological and psychological stress are given in Figure 11.12 and Figure 11.13, respectively.

- There was evidence of a time effect $p<0.001$; no evidence of time by treatment interactions ($p>0.075$) or of overall treatment difference ($p=0.803$).
- There was no evidence of difference in the % change from baseline between the active treatment (GW876008 20 mg) and placebo at any time point analysed, however, there was a statistical evidence of difference between GW876008 200 mg and placebo at 10 min stress time point (estimate 19.97 (95% CI: 2.73,37.21), $p= 0.025$) .
- No effect of stress sequence, baseline or period effect ($p>0.1$) was observed.

The ANOVA results for perception of electrical stimulus % change from baseline are given in Table 11.15 and summarised in Table 11.16 and Table 11.17. The plots of the LS means estimate with 95% CI for the % change from baseline in perception of electrical stimulus in response to physiological and psychological stress are given in Figure 11.14 and Figure 11.15, respectively.

- There was evidence of a time effect and time by treatment interactions ($p<0.02$).
- There was evidence of difference in the % change from baseline between the active treatment (GW876008 20 mg) and placebo at 10 min recovery (estimate -13.80 (95%CI: -26.76,-0.84) $p= 0.039$) and between GW876008 200 mg and placebo at 10 min stress time point (estimate 24.11 (95%CI: 1.70, 46.52) $p=0.039$)
- No effect of stress sequence, baseline or period effect ($p>0.1$) was observed.

The point estimate of the difference in % change from baseline (threshold for pain) between active treatments and placebo is given in the following table.

LS means Estimate of Difference in Percent Change from Baseline: Threshold for Pain

Stress type	Test - Reference	Planned relative time	Test LS mean	Reference LS mean	LS means Estimate of difference (95% Confidence Interval)	P value
PHY	C-A	Stress 10 min	-11.19	-19.92	8.73 (-15.16,32.62)	0.454
		Recovery 10 min	-5.74	4.43	-10.17 (-22.41,2.07)	0.095
	B-A	Stress 10 min	-10.24	-19.92	9.69 (-12.77,32.15)	0.377
		Recovery 10 min	2.72	4.43	-1.70 (-11.82,8.41)	0.715
PSY	C-A	Stress 10 min	1.09	-18.88	19.97 (2.73,37.21)	0.025
		Recovery 10 min	8.42	1.37	7.05 (-3.54,17.63)	0.175
	B-A	Stress 10 min	-17.51	-18.88	1.38 (-14.45,17.20)	0.857
		Recovery 10 min	-6.50	1.37	-7.88 (-16.35,0.60)	0.066

Data Source: Table 11.14

The point estimate of the difference in % change from baseline (perception of electrical stimulus) between active treatments and placebo is given in the following table.

LS means Estimate of Difference in Percent Change from Baseline: Perception of Electrical Stimulus

Stress type	Test - Reference	Planned Relative time	Test LS mean	Reference LS mean	LS means Estimate of Difference (95% Confidence Interval)	P value
PHY	C-A	Stress 10 min	-7.90	-27.00	19.09 (-6.81,45.00)	0.138
		Recovery 10 min	5.25	8.10	-2.85 (-19.12,13.43)	0.710
	B-A	Stress 10 min	-8.91	-27.00	18.08 (-5.64,41.80)	0.125
		Recovery 10 min	-5.70	8.10	-13.80 (-26.76,-0.84)	0.039
PSY	C-A	Stress 10 min	1.33	-22.77	24.11 (1.70,46.52)	0.039
		Recovery 10 min	7.01	-5.57	12.58 (-9.17,34.34)	0.242
	B-A	Stress 10 min	-8.11	-22.77	14.67 (-4.10,33.43)	0.102
		Recovery 10 min	6.64	-5.57	12.21 (-6.49,30.92)	0.187

Data Source: Table 11.17

HAD questionnaire

The correlation plots between HAD assessment scores pre treatment and RMBF at baseline are given in Figure 11.17 and Figure 11.18 for depression and anxiety, respectively, and the correlation values are given in Table 11.19 and Table 11.20 for depression and anxiety, respectively. No significant correlations were observed.

Safety:

There were no deaths or pregnancies reported in this study. One SAE of lymphoma was reported. Details of the SAE are described in the case narrative provided as Attachment 3.

Three out of 9 subjects (33%) experienced a total of 5 AEs during the study (Table 10.11).

[redacted] This subject also experienced a SAE of lymphoma which was reported 31 days after the administration of 20 mg GW876008 and the subject was withdrawn from the study. (See Attachment 3)

[redacted] The adverse event was considered to be mild in intensity.

[redacted]

All the adverse events except lymphoma resolved within 7 days (Table 10.11).

The adverse events are summarised in the following table:

Summary of Adverse Events

All Adverse Events	Total (N= 9)
Any AE, n (%)	3 (33)
Any AE related to investigational product n (%)	2 (22)
Abdominal pain[1]	1 (11)
Diarrhoea[1]	1 (11)
Dry mouth[1]	1 (11)
Gastro oesophageal reflux disease	1 (11)
Lymphoma	1 (11)

Data Source: Table 10.1 and Table 10.4

1. Adverse events considered to be drug-related by the Investigator

Concomitant Medications

Two subjects received concomitant medications. The concomitant medications are summarised in the following table:

Summary of Concomitant Medications

[redacted]

Data Source: Table 10.14

[redacted] The subject was permitted to enter the trial by the Investigator. This subject was a protocol deviation due to the concomitant medication of citalopram. The subject was eventually withdrawn from the study due to a serious adverse event.

Clinical Laboratory Evaluation

Laboratory data including haematology and clinical chemistry were listed. The clinical chemistry (Table 10.6) and the haematology (Table 10.7) results showed no abnormalities of clinical concern.

Electrocardiography

Electrocardiogram (ECG) variables evaluated included heart rate, PR interval, QRS duration, QT interval, QTc (Bazette's) and QTc (Fridericia's). A 12-lead ECG was taken at Screening and a 3-lead ECG was taken at all other ECG time-points. There were no ECG abnormalities that were considered to be of clinical significance by the Investigator (Table 10.9).

Vital Signs

Vital signs measurements comprised heart rate, systolic and diastolic blood pressure. Summary of vital signs is given in Table 10.8. There were no clinically significant abnormalities noted in the vital sign parameters.

Pharmacokinetic:

Blood samples were collected from nine subjects. Table 13.1 lists and summarises the plasma GW876008 concentrations, the times of the sample relative to the dose and the sampling category for summarisation. The observed plasma concentrations relative to those predicted based on a population pharmacokinetic model from healthy volunteers and patients with social anxiety disorder [GlaxoSmithKline Document Number RM2008/00031/00] are plotted in Figure 13.1. Six out of eight concentrations following the 200 mg dose were lower than expected. Four out of nine concentrations following the 20 mg dose were higher than expected. There were four subjects who had samples collected at a similar time relative to dose following each dose that could be directly compared. The plasma concentrations following 20 mg and 200 mg are illustrated for these subjects in Figure 13.2. [redacted]

[redacted] The less than proportional increase in concentration with increasing dose likely represents variability in the rate of absorption and not a lack of dose proportionality.

The relationships between observed plasma concentrations (by sampling category) and RMBF during physical and psychological stress are illustrated in Figure 13.3. Although the number of subjects in each sampling category was small, there did not appear to be any relationship between exposure and RMBF.

The relationships between observed plasma concentrations (by sampling category) and rectal perception during physical and psychological stress are illustrated in Figure 13.4. Although the number of subjects in each sampling category was small, there appeared to be a greater attenuation of effect on rectal perception during physical and psychological stress as concentrations increase for samples collected between 6.25 h and 7.5 h post-dose, but not for samples collected between 3.5 h and 4.5 h post-dose. The number of subjects was too small to characterise this relationship.

Conclusions:

In summary, whilst on placebo, the psychological and physical stressors used in this study induced physiological changes in RMBF and rectal perception/pain thresholds which were consistent with those reported in previous studies, further validating this model for use in pharmacodynamic studies. There was no statistical evidence that GW876008 had any effect on the objective measure of sympathetic outflow RMBF, which was the protocol defined primary endpoint. Failure to demonstrate a statistical effect may have been due to the lack of sufficient power due to less than planned number of subjects entering the study. However, following development of the protocol, it became clear from a pilot study that the most meaningful results may be obtained from the perception and threshold of pain, which were secondary endpoints. This study showed evidence that stress induced rectal hyperalgesia could be attenuated with GW876008 at the dose of 200 mg compared to placebo.

In conclusion, these data provide positive evidence of pharmacological activity of GW876008 in patients with IBS and supports the role of CRF1 antagonism in attenuating stress induced rectal hyperalgesia in IBS patients.

GW876008 appeared to be generally well tolerated demonstrating an acceptable safety profile at the doses tested in IBS patients.

Concentrations of GW876008 were variable and were not well predicted based on pharmacokinetics from healthy volunteers. There may be a relationship between plasma concentrations and rectal perception during physical and psychological stress, but the number of subjects is too low to characterise this relationship.

Date of Report:

May 2008

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