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: SIG110762

Title: A randomised, placebo-controlled, incomplete block, three-way crossover study to evaluate the effect of treatment with repeat inhaled doses of GW870086 on the allergen-induced early and late asthmatic response in subjects with mild asthma.

Rationale: This study was designed to evaluate the efficacy of the inhaled corticosteroid GW870086 using the allergen challenge model in subjects with steroid-naïve atopic bronchial asthma who had demonstrable early and late asthmatic responses.

Phase: IIa.

Study Period: 16-FEB-2009 to 03-NOV-2009.

Study Design: Randomised, double-blind, placebo-controlled, incomplete block, three-way crossover study.

Centres: Four centres in Germany.

Indication: None.

Treatment: Each subject was randomised to three treatment sessions of 13 days (-1/+2 days), inhaled GW870086 0.25, 1 or 3 mg once daily, fluticasone propionate (FP, active control) 0.25 mg twice daily (BID) (AM only on the final day), or placebo. Allergen challenge took place on the final dosing day of each session, and methacholine challenge and sputum induction 1 day later.

Objectives: To evaluate the effect of treatment with repeat inhaled doses of GW870086 once daily for 13 days on the late asthmatic response (LAR) to inhaled allergen in mild asthmatic subjects compared with placebo.

Statistical Methods: The planned sample size of 20 subjects was required to provide approximately 90% power to detect a 50% attenuation from the change from baseline placebo response for minimum LAR, using a two-sided 5% significance level. The subsequent 24 evaluable subjects would provide higher power to detect this effect.
The LAR was measured by forced expiratory volume in 1 second (FEV_1) over 4–10 h after allergen challenge and the early asthmatic response (EAR) as FEV_1 over 0–2 h after allergen challenge. The change from saline baseline minimum and weighted mean LAR and EAR after allergen challenge were analysed using mixed effects models. Estimates for the treatment difference between active doses and placebo for all derived endpoints were calculated, along with two-sided 95% confidence intervals (CIs, calculated using the pooled estimate of variance). The percentage attenuations of the placebo response were also calculated. Change from baseline FEV_1 data, by time, collected during the allergen challenge and non-challenge change from baseline FEV_1 data were also analysed.
Methacholine provocative concentration causing a 20% fall in FEV_1 (PC_{20}) data were log_2 transformed and analysed using a mixed-effects model. The inverse transformed adjusted means and 95% CIs for each treatment group were presented. The difference between the adjusted means was presented on the log_2 scale for treatment comparison (all active treatments versus placebo) together with the associated two-sided 95% CI calculated using the pooled estimate of variance.
Exhaled nitric oxide (NO) concentration was summarised and analysed using a mixed effects model. Sputum cell count data were summarised.

Study Population: Steroid-naïve non-smoking male subjects with mild asthma, aged 18–65 years, with pre-bronchodilator FEV_1 >65% predicted and a positive skin prick test. Subjects had reproducible EAR (FEV_1 fall of ≥20%, 5–30 minutes after allergen challenge) and LAR (FEV_1 fall of ≥15% on at least three occasions, 4–10 h after challenge). Subjects showed a methacholine PC_{20} of <8 mg/mL.

Number of Subjects:	**Total**
Planned N	24
Dosed N	24
Completed n (%)	24 (100)
Demographics	**Total**
N (All Subjects)	24
Females: Males	All male
Mean age in years (standard deviation)	39.4 (11.25)
Mean weight in kg (standard deviation)	83.15 (7.874)
White n (%)	24 (100)

Pharmacodynamics: A summary of the statistical analysis of allergen challenge absolute change from saline baseline in minimum and weighted mean LAR on Day 13 is presented below.

Derived endpoint	Treatment	n	Treatment difference (L) (vs. placebo)		Attenuation of placebo response (%)
			Estimate	95% CI	
Minimum LAR	GW870086 0.25 mg	12	0.240	(0.031, 0.449)	26.6
	GW870086 1 mg	11	0.265	(0.053, 0.477)	29.3
	GW870086 3 mg	12	0.456	(0.255, 0.657)	50.5
	FP 0.25 mg BID	12	0.526	(0.319, 0.733)	58.3
Weighted mean LAR	GW870086 0.25 mg	12	0.210	(0.013, 0.407)	38.1
	GW870086 1 mg	11	0.154	(-0.046, 0.354)	28.0
	GW870086 3 mg	12	0.303	(0.113, 0.492)	55.0
	FP 0.25 mg BID	12	0.404	(0.209, 0.599)	73.4

A summary of the statistical analysis of allergen challenge absolute change from saline baseline in minimum and weighted mean EAR on Day 13 is presented below.

Derived endpoint	Treatment	n	Treatment difference (L) (vs. placebo)		Attenuation of placebo response (%)
			Estimate	95% CI	
Minimum EAR	GW870086 0.25 mg	12	-0.025	(-0.302, 0.253)	-1.8
	GW870086 1 mg	11	0.106	(-0.176, 0.387)	7.9
	GW870086 3 mg	12	0.239	(-0.028, 0.506)	17.8
	FP 0.25 mg BID	12	0.534	(0.260, 0.809)	39.9
Weighted Mean EAR	GW870086 0.25 mg	12	0.054	(-0.145, 0.253)	6.6
	GW870086 1 mg	11	0.026	(-0.176, 0.228)	3.1
	GW870086 3 mg	12	0.180	(-0.011, 0.371)	22.1
	FP 0.25 mg BID	12	0.350	(0.153, 0.548)	43.0

Non-challenge spirometry data showed that all active groups tended to have larger values than placebo for FEV_1 change from baseline at all days. The changes were more notable in the GW870086 3 mg and FP 0.25 mg BID groups. The mean differences (in L) versus placebo on Days 7, 13 and 14 were 0.297 (95% CI 0.100 to 0.493), 0.256 (95% CI 0.083 to 0.429) and 0.462 (95% CI 0.262 to 0.662), respectively, in GW870086 3 mg, and 0.323 (95% CI 0.125 to 0.520), 0.229 (95% CI 0.057 to 0.402) and 0.372 (95% CI 0.172 to 0.572), respectively, in FP 0.25 mg BID.

A summary of the statistical analysis of methacholine challenge PC_{20} data on Day 14 is presented below.

Treatment	n	Treatment doubling doses difference (vs. placebo)	
		Estimate	95% CI
GW870086 0.25 mg	9	-0.32	(-1.30, 0.66)
GW870086 1 mg	9	0.27	(-0.73, 1.28)
GW870086 3 mg	11	1.28	(0.36, 2.19)
FP 0.25 mg BID	10	1.79	(0.84, 2.75)

A summary of exhaled NO data at Day 13 is presented below.

Treatment	n	Adjusted geometric mean concentration of exhaled NO (ppb)		Ratio of geometric means/placebo	
		Estimate	95% CI	Estimate	95% CI
Placebo	24	52.91	(46.10, 60.72)		
GW870086 0.25 mg	12	37.76	(30.98, 46.02)	0.71	(0.56, 0.90)
GW870086 1 mg	11	34.95	(28.97, 42.16)	0.66	(0.53, 0.82)
GW870086 3 mg	12	31.18	(25.62, 37.95)	0.59	(0.47, 0.74)
FP 0.25 mg BID	12	23.57	(19.54, 28.43)	0.45	(0.36, 0.55)

Mean (95% CI) eosinophil percentage cell count was 17.9% (10.8, 25.0%) following placebo administration, 12.2% (-3.4, 27.9%) with GW870086 0.25 mg, 6.6% (2.3, 10.8%) with 1 mg, 2.8% (-1.7, 7.2%) with 3 mg and 5.4% (0.5, 10.3%) with FP 0.25 mg BID.

Safety results: Adverse event and serious adverse event (SAE) data were recorded from the start of investigational product and until the follow-up contact. Any SAEs related to study participation or related to a GSK concomitant medication were to be recorded from the time a subject consented to participate in the study up to and including the follow-up contact. The most frequently reported AEs are summarised below.

Adverse Events	Placebo	GW870086			FP 0.25 mg	Total
		0.25 mg	1 mg	3 mg		
N (All Subjects)	24	12	12	12	12	24
No. subjects with AEs, n (%)	8 (33)	4 (33)	7 (58)	4 (33)	3 (25)	18 (75)
Most frequent AEs (more than one subject in total)						
Headache	3 (13)	1 (8)	6 (50)	0	1 (8)	9 (38)
Nasopharyngitis	2 (8)	0	0	3 (25)	0	5 (21)
Bronchospasm	1 (4)	2 (17)	0	1 (8)	0	2 (8)
Serious Adverse Events: There were no SAEs.						