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: SIG114749

Title: A Phase II Randomised, Double-Blind, Placebo-Controlled, Parallel Group, Multicentre Study to determine the efficacy and dose response of repeat inhaled doses of GW870086X on FEV1 in adults with Persistent Asthma

Rationale: GW870086X could provide a once daily (OD) inhaled steroid treatment for asthma with a reduced side effect profile as it has shown superior selectivity for the glucocorticoid receptor over the progesterone and mineralocorticoid receptors compared with fluticasone propionate. The purpose of this study was to evaluate the efficacy and safety of GW870086X in adults with mild to moderate asthma after 4 weeks of treatment using doses that were deemed safe and predicted to significantly affect forced expiratory volume in 1 second (FEV1).

Phase: II

Study Period: 14 December 2010–19 August 2011

Study Design: Randomised, double-blind, placebo-controlled, parallel group, multicentre, adaptive design.

Centres: Seven centres in Germany, three centres in South Africa and one centre in Bulgaria.

Indication: Persistent asthma.

Treatment: Subjects were initially randomised to receive placebo or GW870086X 2 mg or 4 mg OD in the morning for 27 $\pm$ 2 days. A 3 mg dose of GW870086X was added after an interim analysis to further investigate the dose response.
The total duration of a subject's participation, from screening to follow-up, was 9–12 weeks. This consisted of a screening visit within 2 weeks prior to the start of the 4-week run-in period, a 27-day ($\pm$ 2 days) treatment period and a follow-up visit 1–2 weeks after the final dose of study medication.

Objectives: To determine the efficacy and dose response of repeat inhaled doses of GW870086X OD, after 28 days, on FEV1 in mild to moderate asthmatics, compared with placebo.

Statistical Methods: The primary endpoint was analysed by mixed effects model fitted baseline by time, treatment by time, country, sex, age and body mass index as fixed effects with time fitted as a repeated measure.
Sensitivity analyses were performed for the analysis of the primary endpoint. These included repeating the primary analysis on the Per-Protocol Population.
Similar analyses were performed for morning (AM) PEFR and afternoon (PM) PEFR as for the primary endpoint FEV1. The change from baseline PEFR for each of the doses was calculated with 95% confidence intervals for each weekly time point separately for each of the analyses. No sensitivity analyses were run for PEFR.
Safety data were summarised descriptively.
Trough concentration samples collected on the specified days were to be used to demonstrate maintenance of steady-state systemic exposure to GW870086 at expected concentrations based on historical data. Plasma GW870086 concentration-time data were to be presented in graphical and/or tabular form and were to be summarised descriptively.
The 'Intent-to-Treat Population' was defined as all subjects who received at least one dose of study medication and had at least one post-dose FEV1 or PEFR assessment. Subjects were analysed by the treatment they received rather than the treatment they were randomised to receive. The primary analysis was conducted on the Intent-to-Treat population.
The 'All Subjects Population' was defined as all subjects who received at least one dose of study medication.
A 'Per-Protocol' population was defined excluding protocol deviators, of which there were two, who both had <60% predicted normal FEV1 at randomisation. The Per-Protocol population, as well as excluding protocol deviators, excluded all subjects' time points for FEV1 and PEFR when they administered rescue medication within 4 h of their assessment.
All 135 subjects were included in the 'All Subjects' and 'Intent-to-Treat' populations; 133 subjects were included in the Per-Protocol population.

Study Population: Consenting, non-smoking males aged between 18 and 65 years using appropriate contraception and females of non-childbearing potential aged between 18 and 65 years with a documented history of bronchial asthma and a best FEV1 of 60 to <85% of the predicted normal value at screening were eligible. Men had to be $\geq$50 kg, women had to be $\geq$45 kg and both had to have a body mass index within the range 18.5–29.0 kg/m^2 (inclusive).

Number of Subjects:		**GW870086X**			
	Placebo	**2 mg**	**3 mg**	**4 mg**	**Total**
Planned N					132

Randomised N	33	33	33	36	135
Completed n (%)	32 (97)	33 (100)	31 (94)	35 (97)	131 (97)
Total Number Subjects Withdrawn N (%)	1 (3)	0	2 (6)	1 (3)	4 (3)
Withdrawn due to Adverse Events n (%)	1 (3)	0	0	0	1 (<1)
Reached Protocol-Defined Stopping Criteria n (%)	0	0	2 (6)	0	2 (1)
Withdrew Consent n (%)	0	0	0	1 (3)	1 (<1)
Demographics					
N	33	33	33	36	135
Females: Males	8:25	6:27	9:24	3:33	26:109
Mean Age in Years (range)	46.0 (22–65)	44.3 (18–62)	44.9 (21–64)	39.4 (18–59)	43.5 (18–65)
Mean Weight in Kg (range)	80.81 (59.2–105.0)	82.54 (65.0–106.0)	78.40 (50.0–108.3)	79.43 (53.0–101.0)	80.28 (50.0–108.3)
Mean Height in Cm (range)	177.2 (153–196)	179.3 (160–203)	175.0 (154–192)	178.3 (160–196)	177.5 (153–203)
Mean Body Mass Index in kg/m^2 (range)	25.67 (20.8–31.4)	25.67 (21.9–28.8)	25.46 (18.6–29.4)	24.93 (18.9–28.8)	25.42 (18.6–31.4)
Not Hispanic or Latino n (%)	33 (100)	33 (100)	33 (100)	36 (100)	135 (100)
African American/African Heritage	4 (12)	1 (3)	1 (3)	1 (3)	7 (5)
Asian – East Asian Heritage	0	0	0	1 (3)	1 (<1)
White – White/Caucasian/ European Heritage	29 (88)	32 (97)	32 (97)	34 (94)	127 (94)

Efficacy Endpoints: Improvements were observed in FEV1 at Week 4 for each of the doses of GW870086X compared with placebo. The average 2 mg and 4 mg improvements compared with placebo were comparable at 172 mL (95% confidence interval (15, 329)) and 159 mL (95% confidence interval (1, 316)), which were both statistically significant at the 5% level as can be seen from the confidence interval. The average 3 mg improvement compared with placebo was slightly lower at 105 mL (95% confidence interval (-53, 263)), which was not statistically significant. These data are presented in the table below.

Comparison	Estimate	Least Square Means		95% CI	p-value	SD	Probability (%) Treatment Difference		
		Test	Ref				<0.05	>0.1	>0.15
2 mg – Placebo Week 1	0.105	0.131	0.025	-0.038, 0.248	0.1478	0.291	22.25	52.83	26.71
2 mg – Placebo Week 2	0.160	0.160	-0.001	0.003, 0.318	0.0462	0.320	8.31	77.53	55.09
2 mg – Placebo Week 3	0.146	0.139	-0.007	-0.012, 0.303	0.0702	0.321	11.51	71.65	47.82
2 mg – Placebo Week 4	0.172	0.142	-0.030	0.015, 0.329	0.0323	0.319	6.24	81.72	60.83
3 mg – Placebo Week 1	0.059	0.084	0.025	-0.084, 0.202	0.4158	0.291	45.05	28.52	10.40
3 mg – Placebo Week 2	0.074	0.073	-0.001	-0.084, 0.231	0.3548	0.320	38.18	37.17	16.96
3 mg – Placebo Week 3	0.069	0.063	-0.007	-0.089, 0.227	0.3891	0.321	40.55	34.97	15.59
3 mg – Placebo Week 4	0.105	0.075	-0.030	-0.053, 0.263	0.1919	0.319	24.64	52.38	28.55
4 mg – Placebo Week 1	0.033	0.059	0.025	-0.110, 0.177	0.6449	0.291	59.02	17.93	5.39
4 mg – Placebo Week 2	0.112	0.111	-0.001	-0.045, 0.270	0.1618	0.320	21.80	56.00	31.66
4 mg – Placebo Week 3	0.124	0.117	-0.007	-0.034, 0.282	0.1237	0.321	17.76	61.76	37.21
4 mg – Placebo Week 4	0.159	0.128	-0.030	0.001, 0.316	0.0484	0.319	8.61	76.94	54.33

CI=confidence interval; SD=standard deviation.

A summary of the statistical analysis of change from baseline PEFR (L/min) is presented in the table below.

Comparison	Estimate	Least Square Means		95% CI	p-value	SD
		Test	Ref			
AM Dosing						
2 mg – Placebo Week 1	19.57	8.26	-11.31	4.77, 34.36	0.0100	28.146
2 mg – Placebo Week 2	33.86	26.75	-7.11	17.26, 50.47	<.0001	32.337
2 mg – Placebo Week 3	31.24	30.51	-0.74	13.49, 48.99	0.0007	34.740
2 mg – Placebo Week 4	27.98	22.33	-5.65	9.39, 46.57	0.0035	36.198
3 mg – Placebo Week 1	5.75	-5.56	-11.31	-8.80, 20.29	0.4354	28.146
3 mg – Placebo Week 2	10.30	3.19	-7.11	-6.14, 26.74	0.2170	32.337
3 mg – Placebo Week 3	14.96	14.23	-0.74	-2.73, 32.65	0.0966	34.740
3 mg – Placebo Week 4	17.68	12.03	-5.65	-0.90, 36.26	0.0621	36.198
4 mg – Placebo Week 1	10.58	-0.72	-11.31	-3.99, 25.15	0.1530	28.146
4 mg – Placebo Week 2	18.09	10.98	-7.11	1.82, 34.37	0.0296	32.337
4 mg – Placebo Week 3	17.91	17.17	-0.74	0.56, 35.26	0.0431	34.740
4 mg – Placebo Week 4	21.95	16.31	-5.65	3.76, 40.14	0.0184	36.198
PM Dosing						

2 mg – Placebo Week 1	28.37	14.74	-13.63	12.00, 44.74	0.0008	32.944
2 mg – Placebo Week 2	48.99	32.48	-16.51	31.63, 66.35	<.0001	35.148
2 mg – Placebo Week 3	40.52	29.53	-10.99	22.30, 58.75	<.0001	36.687
2 mg – Placebo Week 4	41.31	28.10	-13.20	20.67, 61.94	0.0001	41.660
3 mg – Placebo Week 1	19.96	6.33	-13.63	3.49, 36.42	0.0179	32.944
3 mg – Placebo Week 2	34.26	17.75	-16.51	16.80, 51.73	0.0002	35.148
3 mg – Placebo Week 3	28.73	17.74	-10.99	10.37, 47.08	0.0024	36.687
3 mg – Placebo Week 4	34.60	21.39	-13.20	13.66, 55.54	0.0014	41.660
4 mg – Placebo Week 1	11.14	-2.49	-13.63	-5.33, 27.62	0.1831	32.944
4 mg – Placebo Week 2	26.31	9.80	-16.51	8.89, 43.73	0.0034	35.148
4 mg – Placebo Week 3	25.77	14.78	-10.99	7.55, 43.99	0.0059	36.687
4 mg – Placebo Week 4	27.92	14.72	-13.20	7.31, 48.54	0.0083	41.660

CI=confidence interval; SD=standard deviation.

The total numbers of salbutamol puffs taken over the treatment period are presented below.

	N	n	n*	Mean	SD	Median	Percentiles		Min	Max
							25%	75%		
Placebo	33	29	4	57.6	43.6	52.0	18.0	89.0	4	149
2 mg	33	28	5	32.4	30.5	23.5	9.5	39.0	4	124
3 mg	33	27	6	25.6	30.8	16.0	4.0	36.0	1	140
4 mg	36	30	6	18.6	16.3	13.5	6.0	21.0	1	56

n=number of subjects who did take salbutamol; n*=number of subjects who did not take salbutamol; SD=standard deviation

Safety results: Adverse event and serious AE (SAE) data were collected and recorded in the electronic case report form starting on Day 1 of the treatment period and continuing until the follow-up visit. A summary of all AEs reported by more than one subject is presented below. One subject on placebo withdrew from the study due to AEs of nasopharyngitis and asthma; no other withdrawals due to AEs were reported. There were no treatment-emergent clinically significant changes in vital signs, clinical laboratory or electrocardiogram results that were considered to be associated with GW870086X.

Adverse Events:		**GW870086X**		
	Placebo	**2 mg**	**3 mg**	**4 mg**
N	33	33	33	36
No. subjects with AEs n (%)	18 (55)	12 (36)	13 (39)	16 (44)
Most Frequent AEs				
Headache	4 (12)	8 (24)	6 (18)	5 (14)
Nasopharyngitis	5 (15)	1 (3)	1 (3)	3 (8)
Cough	1 (3)	3 (9)	1 (3)	1 (3)
Nausea	3 (9)	1 (3)	0	1 (3)
Oropharyngeal pain	3 (9)	0	1 (3)	0
Dysphonia	2 (6)	0	1 (3)	1 (3)
Malaise	2 (6)	0	0	0

Serious Adverse Events, n (%) [n considered by the Investigator to be related, possibly related or probably related to study medication]: no SAEs were reported in this study.

Pharmacokinetic Endpoints: A summary of GW870086X plasma pharmacokinetic concentration-time data (pg/mL) is presented below.

Dose	N	Visit	n	No. imputed	Mean	SD	Median	Min	Max
2 mg	33	Week 1 pre-dose	33	12	63.11		58.10	0.0	216.0
		Week 2 pre-dose	32	8	67.56	55.516	61.40	0.0	203.9
		Week 3 pre-dose	33	12	56.72		56.40	0.0	171.0
		Week 4 pre-dose	33	13	50.28		58.40	0.0	160.4
		Overall	131	45	59.36		58.40	0.0	216.0
3 mg	33	Week 1 pre-dose	33	10	68.90		57.60	0.0	348.3
		Week 2 pre-dose	33	11	63.62		61.50	0.0	253.8
		Week 3 pre-dose	31	5	91.46	80.515	86.50	0.0	419.4
		Week 4 pre-dose	30	3	92.70	67.196	81.50	0.0	320.8

		Overall	127	29	78.66	70.977	68.90	0.0	419.4
4 mg	36	Week 1 pre-dose	35	4	95.01	73.190	63.00	0.0	294.7
		Week 2 pre-dose	35	3	113.89	77.110	91.30	0.0	330.2
		Week 3 pre-dose	34	2	131.22	96.769	83.65	0.0	360.4
		Week 4 pre-dose	34	3	131.84	98.570	93.25	0.0	337.6
		Overall	138	12	117.79	87.357	86.60	0.0	360.4